Correspondence. Surnames, 'Chamberlain' to 'Gyte'

Contributors

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Publication/Creation

2004-2005

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Tel: +44 (0) 20 7679 8125
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19th March 2004

Dear Prfoessor Chamberlain

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004
2.00 pm – 6.00 pm

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is organising a Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15th June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1 2BE. Dr Edmund Hey has kindly agreed to chair the meeting and Sir Iain Chalmers is assisting us in the organisation.

Sir Iain Chalmers has recommended that we invite you to this meeting and we would be delighted to have you join us.

As you know, these seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history. I enclose a flyer of our recent publications to illustrate the range of topics we cover.

Continued/... Page 2

We are in the process of inviting senior scientists, clinicians, and representatives from relevant organisations to attend the meeting and hope to promote a lively discussion.

We will be providing further details in due course and would particularly appreciate, at this stage, suggestions of possible participants.

I look forward to hearing from you and do hope you will be able to accept this invitation.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

(W) - rec'd 11 May '04

PRIFYSGOL CYMRU ABERTAWE
Yr Ysgol Glinigol
Abertawe, SA2 8PP, Cymru

UNIVERSITY OF WALES SWANSEA
The Clinical School
Swansea, SA2 8PP, UK
HISTORY OF MEDICINE UNIT

Reply to: Professor Geoffrey Chamberlain, Apothecaries Lecturer
Tel: 01792 285349 : Fax: 01792 285507

16th April 2004

Dr Daphne Christie
Snr Research Assistant to Dr T Tansey
The Wellcome Trust Centre for the
History of Medicine
University College London
24 Everholt Street
LONDON NW1 1AD

Dear Dr Christie

RE: WITNESS SEMINAR: PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY ASSOCIATED WITH PRETERM BIRTH
TUESDAY 15.06.04. 2.00pm – 6.00 pm

Thank you very much for inviting me to this seminar. Unfortunately, I will be away at that time and unable to attend.

Yours sincerely

pp Sian M. Roberts

PROFESSOR GEOFFREY CHAMBERLAIN MD FRCS FRCOG

YMDDIRIEDOLAETH GIG ABERTAWE SWANSEA NHS TRUST

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21 April 2004

Dear Professor Chamberlain

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 30th March 2004 2.00 pm – 6pm

We wrote to you on 19th March, inviting you to attend the above meeting. As we have not had a reply, but have been experiencing difficulties with our post, our original letter, or your reply, may therefore have gone astray. We enclose a copy of that letter and look forward to hearing from you.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

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27 April 2004

Dear Professor Chamberlain

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004 2.00 pm – 6pm

We wrote to you on 21st April, enclosing our original invitation letter to the above meeting, but the date of the meeting on the reminder letter was incorrect. Please note that the date of the meeting is Tuesday 15th June 2004.

Yours sincerely

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey

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Wendy Kutner

To: Chew ,Dr Michael
Subject: RE: Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth - Tuesday 15 June 2004

Dear Dr Chew
Thank you for your e-mail. We have added both you and your colleague to the list of participants. We look forward to seeing you at the meeting.
With best wishes
Daphne Christie

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
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-----Original Message-----
From: Chew ,Dr Michael [mailto:m.Chew@wellcome.ac.uk]
Sent: 12 May 2004 16:42
To: w.kutner
Subject: Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth - Tuesday 15 June 2004

Dear Wendy,

Just to confirm the request for two to attend the Witness Seminar on June 15th.

Dr Michael Chew
Tropical Medicine Programme
The Wellcome Trust

Dr Quen Mok
Paediatric Intensive Care Unit
Great Ormond Street Hospital for Children NHS Trust

Many thanks.

Michael

Dr Michael Chew
Science Programme Officer
Tropical Medicine Programme
The Wellcome Trust
183 Euston Road
London NW1 2BE
Tel: +44 20 76118856
Fax: +44 20 76117288
Email: m.chew@wellcome.ac.uk

Professor John Coghlan
Dr Marelyn Wintour
Florey Institute
University of Melbourne
AUSTRALIA

(e) coghlan@mail.vicnet.net.au

Dr Daphne Christie
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30 March 2004

Dear Professor Coghlan and Dr Wintour

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004 2.00 pm – 6.00 pm

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is organising a Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15 June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1 2BE. Dr Edmund Hey has kindly agreed to chair the meeting and Sir Iain Chalmers is assisting us in the organisation.

These seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history.

We have drawn up a list of possible participants, including clinicians and representatives from relevant organisations, and would like to include physiologists/endocrinologists from the 1960s and early 70s. Sir Graham Liggins is unable to attend but we hope to have Marc Keirse to introduce his work. Professor Gavin Vinson has suggested I contact you to see whether you would be able to help with names of scientists, (preferably based in England, as we don't have the means to fund overseas travel) particularly those who were involved in the work on sheep during the 1960s.

I look forward to hearing from you and do hope you will be able to help.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

Dr Daphne Christie

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 31 March 2004 08:35
To: Marelyn Wintour-Coghlan
Subject: RE: Witness Seminar

Thank you for this information. We will follow up your suggestions.
With best wishes,
Daphne Christie

-----Original Message-----
From: Marelyn Wintour-Coghlan [mailto:mwc@med.monash.edu.au]
Sent: 31 March 2004 01:21
To: d.christie@ucl.ac.uk
Subject: Witness Seminar

Dear Dr Christie, The people who know much of the action of glucocorticoids on in utero maturation currently are Professor Abigail Fowden and Dr Dino Guissani, both in Cambridge Physiology (alf1000@cam.ac.uk; dag26@cam.ac.uk). Of the 'oldies' I don't quite know who is still around--there were some at the Mordun at Cardiff, and Mark Hanson (m.hanson@soton.ac.uk) at Southampton might be able to help you.

Best Wishes, E>Marelyn Wintour-Coghlan, PhD,D.Sc FAA--Professor , Physiology, Monash, Clayton, Vic3800

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 31 March 2004 08:36
To: Wendy
Subject: FW: Witness Seminar

please add these names to the grid and draft a letter to Mark Hanson.
Thanks, Daphne

-----Original Message-----
From: Marelyn Wintour-Coghlan [mailto:mwc@med.monash.edu.au]
Sent: 31 March 2004 01:21
To: d.christie@ucl.ac.uk
Subject: Witness Seminar

Dear Dr Christie, The people who know much of the action of glucocorticoids on in utero maturation currently are Professor Abigail Fowden and Dr Dino Guissani, both in Cambridge Physiology (alf1000@cam.ac.uk; dag26@cam.ac.uk). Of the 'oldies' I don't quite know who is still around--there were some at the Mordun at Cardiff, and Mark Hanson (m.hanson@soton.ac.uk) at Southampton might be able to help you.

Best Wishes, E>Marelyn Wintour-Coghlan, PhD,D.Sc FAA--Professor , Physiology, Monash, Clayton, Vic3800

Wendy Kutner

To: coghlan@mail.vicnet.net.au
Subject: FW: Witness Seminar: Prenatal corticosteriods - 15 June 2004

CortiCOGHLAN+WINTOURltr.doc

Dear Professor Coghlan, Please see e-mail below and attachment. Thank you. Yours sincerely, Wendy Kutner

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
The Wellcome Trust Centre
for the History of Medicine at UCL
Euston House
24 Eversholt Street
LONDON NW1 1AD

Tel: 020 7679 8106
Fax: 020 7679 8193
w.kutner@ucl.ac.uk
www.ucl.ac.uk/histmed

-----Original Message-----
From: Wendy Kutner [mailto:w.kutner@ucl.ac.uk]
Sent: 30 March 2004 14:55
To: coghlan@mail.vicnet.net.au
Cc: Daphne Christie
Subject: Witness Seminar: Prenatal corticosteriods - 15 June 2004

Dear Professor Coghlan, Your name and e-mail address, and your wife's name have been sent to us by Professor Gavin Vinson in connection with the above meeting. Please see the attached letter. Yours sincerely, Wendy Kutner

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
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Wendy Kutner

To: coghlan@mail.icnet.net.au
Subject: Witness Seminar: Prenatal corticosteriods - 15 June 2004

CortiCOGHLAN+WINTOURltr.doc

Dear Professor Coghlan, Your name and e-mail address, and your wife's name have been sent to us by Professor Gavin Vinson in connection with the above meeting. Please see the attached letter. Yours sincerely, Wendy Kutner

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
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Professor Brian Cooke
2 Prospect Lane
Harpenden AL5 2PL

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24 March 2004

Dear Professor Cooke

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004 2.00 pm – 6.00 pm

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is organising a Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15 June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1 2BE. Dr Edmund Hey has kindly agreed to chair the meeting and Sir Iain Chalmers is assisting us in the organisation.

These seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history.

We have drawn up a list of possible participants, including clinicians and representatives from relevant organisations, and would like to include physiologists/endocrinologists from the 1960s and early 70s. Sir Graham Liggins is unable to attend but we hope to have Marc Keirse to introduce his work. I am therefore writing to ask if you might be able to help with names of scientists, particularly those who were involved in the work on sheep during the 1960s.

I do hope you will be able to help.

I look forward to hearing from you.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

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UCL

Professor Patricia Crowley FRCPI
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20 February 2004

Professor Crowley

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004
2.00 pm – 6.00 pm

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is organising a Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15th June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1. Sir Iain Chalmers is assisting us in the organization of the meeting.

Sir Iain has recommended that we invite you to this meeting and we would be delighted to have you join us.

These seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history. I enclose a copy of the introduction to the first volume of our published transcripts, which will tell you a little more about these seminars, and a flyer of our recent publications to illustrate the range of topics we cover.

Continued/... Page 2

We are in the process of inviting senior scientists, clinicians, and representatives from relevant organisations to attend the meeting and hope to promote a lively discussion. We will be providing further details in due course and would particularly appreciate, at this stage, suggestions of possible participants.

I look forward to hearing from you and do hope you will be able to accept this invitation.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

Professor Patricia Crowley FRCPI
Department of Obstetrics & Gynaecology
Coombe Women's Hospital
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4 March 2004

Dear Professor Crowley

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004
2.00 pm – 6.00 pm

We have been informed by Sir Iain Chalmers that you would like to accept our invitation to attend the above meeting, and that our invitation may have been lost in the post, as you have not received it.

I am therefore enclosing a copy of our original invitation, with attachments, for your files and to let you know that we are delighted you are able to attend.

We will be in touch again nearer the meeting.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

cc Sir Iain Chalmers

The Wellcome Trust Centre for the History of Medicine at University College London

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26 April 2004

Dear Professor Crowley

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004, 2pm–6pm

We are delighted that you are able to attend the above meeting and are happy to tell you that plans are proceeding well. A copy of our publicity material is enclosed and I will be sending you a draft programme in due course. A full attendance list will be available at the meeting.

We will be asking some participants to "start the ball rolling" by saying a few words on specific subjects, as we like to prime a few people to lead off the discussions, although there will be ample opportunity to contribute throughout the meeting. We do not show slides or overheads at the meetings, as we wish to encourage informal interchange and conversation. If however, you would like any material to be available to the audience, we could photocopy a diagram or article for you, and leave a copy on every chair.

Please do not hesitate to contact either myself or Mrs Wendy Kutner 020 7679 8106 if you have any queries prior to the meeting.

We very much look forward to seeing you at the meeting.

Yours sincerely

Wendy Kutner pp

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

enc.

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Fax: +44 (0) 20 7679 8193

12 May 2004

Dear Professor Crowley

Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Venue: Franks II, Mezzanine Floor, Wellcome Building, 183 Euston Road, London NW1
Tuesday 15th June 2004: 2.00 pm – 6pm

We are delighted that you are able to attend the above meeting and are happy to tell you that plans for the meeting are proceeding well. A copy of our publicity material has already been sent to you under separate cover and I am now enclosing a draft programme. A full attendance list will be available at the meeting.

We would be very grateful if you would be prepared for the Chairman to call upon you to say a few words, for about 5 minutes, on 'The systematic review of RCTs and the NIH consensus conference'. We like to prime a few people to lead off the discussions, although there will be ample opportunity to contribute throughout the meeting. We do not show slides or overheads at the meetings, as we wish to encourage informal interchange and conversation. If however, you would like any material to be available to the audience, we could photocopy a diagram or article for you, and leave a copy on every chair.

We do not have the funds to assist with your travel from overseas, but whilst you are in the UK, The Wellcome Trust Centre for the History of Medicine at University College London will reimburse your return travel costs to the meeting only if supported by suitable receipts. They are inflexible in this matter.

We would also like to arrange accommodation for you at The Hotel Ibis London Euston for the night of the Seminar, Tuesday 15th June, and I would be most grateful if you could contact me upon receipt of this letter, d.christie@ucl.ac.uk or 0044207 679 8125 to confirm your requirements. Again, please note that University College London will only pay for accommodation reserved and authorised by us.

Continued/ Page 2 …

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Dr Tilli Tansey and I would like to invite you to join us for an early supper at a local restaurant after the meeting. We should be finished by 9pm to give you ample time to return to the hotel. Please let me know whether you are able to attend the supper (d.christie@ucl.ac.uk). You may also contact Mrs Wendy Kutner (w.kutner@ucl.ac.uk) 0044 207679 8106 or myself if you have any queries on the above or would like any further information.

Please note that informal drinks will be served immediately after the meeting. We look forward to seeing you on the 15th June.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

enc

The Wellcome Trust Centre for the History of Medicine at University College London

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16 June 2004

Dear Dr Crowley

The Wellcome Trust History of Twentieth Century Medicine Group Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with pretern birth

May I say on behalf of The History of Twentieth Century Medicine Group and the co-organiser, how grateful we are to you for your contributions to yesterday's meeting? It really was a splendid occasion, and we hope that you enjoyed it as much as those of us who were observers.

As mentioned in previous correspondence and at the meeting, the taped proceedings of the meeting will now be sent for transcription, and we hope to have a draft manuscript to send you in about six months time for your comments. Ultimately we intend to publish an edited version of the proceedings, and you will be sent a copyright assignment form and final proof before publication.

We particularly want to thank you for travelling from Dublin to attend the meeting. Your personal contribution was much appreciated and added to the success of the meeting.

Yours sincerely

Daphne Christie

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

The Wellcome Trust Centre for the History of Medicine at University College London is funded by the Wellcome Trust, which is a registered charity, no. 210183. Histmed logo images courtesy *Wellcome Library*, London.

Professor Patricia Crowley FRCPI,
Department of Obstetrics & Gynaecology,
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7 December 2004

Dear Dr Crowley

Witness Seminar: Prenatal Corticosteroids for reducing Morbidity and Mortality

I enclose a draft transcript of the Witness Seminar on '**Prenatal Corticosteroids for reducing Morbidity and Mortality**' to which you contributed. We intend to publish a version of the transcript in November 2005 under the auspices of the Wellcome Trust Centre for the History of Medicine at UCL.

I would be most grateful if you could check your own contributions for general sense, accuracy and typographical mistakes. We do not encourage extensive alterations, as the purpose of these publications is to retain the freshness and informality of the meeting. However, any additional information can be added as a footnote and you may like to suggest such material Please mark all corrections clearly on this copy and return it to me by **Monday 10 January** Earlier published volumes in the series can be viewed on our website, www.ucl.ac.uk/histmed/witnesses.html

If you would like to comment on any other part of the transcript, other than the corrections to your own contribution, please feel free to do so.

- Please provide a 2–3 sentence biographical piece for inclusion in the notes at the end of the volume including year of birth and dates of major appointments.
- Please sign and return the standard form assigning copyright to the Wellcome Trust.
- Please let us know if you do not want your name included in our twice-yearly marketing mailings.
- We would like to include illustrations of early work in the volume. If you have any suitable images or figures, please include these with the pages. They will be carefully scanned and returned in protective packaging.
- A final proof version, incorporating the changes made by all the participants, added footnotes, and any queries will be sent to you in **September 2005** for return within a week. **At this stage only minor corrections, such as those of a typographical nature, will be possible.**

The tapes, earlier versions of the transcript, and any additional correspondence generated by the editorial process, will be deposited in Wellcome Library. A version of the transcript will also be mounted on the Wellcome Trust Centre's website shortly after publication.

I look forward to hearing from you.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

THE WELLCOME TRUST

WITNESS SEMINARS

COPYRIGHT ASSIGNMENT

Witness seminars are intended to address issues of medical–historical interest in the latter half of the twentieth century. The entire proceedings are recorded and transcribed by the Wellcome Trust with a view to publication to generate interest in, and provide material sources for, the study of significant events in recent medical history. As copyright in anything you said during the proceedings belongs to you (copyright in the recording of the proceedings belonging to the Wellcome Trust), we would be grateful if you would complete this form to enable the Wellcome Trust to use your contribution in the manner and for the purposes outlined above.

****

1. NAME Dr Patricia Crowley FRCPI

2. ADDRESS
Department of Obstetrics & Gynaecology, Coombe Women's Hospital, Dublin 8, EIRE

3. WITNESS SEMINAR: Prenatal Corticosteroids for Reducing Morbidity and Mortality
15 June 2004

4. ASSIGNMENT

I confirm that I am the author and legal owner of my contribution to the proceedings of the Witness Seminar and of any comments I may have made on any draft transcript ("my Contribution"), and I assign to the Trustee of the Wellcome Trust ("the Trust") the copyright in my Contribution.

5. SOUND RECORDING

I confirm that the entire copyright and all other rights in the sound recording made of my Contribution by the Trust at the Witness Seminar ("the Sound Recording") and the transcript made of the Sound Recording belong to the Trust for the full period of copyright including all renewals and extensions.

6. PUBLICATION

I acknowledge the right of the Trust as assignee of the copyright in my Contribution to publish my Contribution in whole or in part.

I acknowledge the right of the editor of any publication of my Contribution to edit my Contribution provided that my approval of any changes made by the editor will be obtained (such approval not to be unreasonably withheld).

7. USE OF MY CONTRIBUTION

I reserve the right to make use of my Contribution, having first obtained the permission of the Trust for me to do so (such permission not to be unreasonably withheld) and I confirm that in any such use I will acknowledge the Trust.

Signed..... Date.....

Sent to address from Chelmers 15/7/05

Professor Patricia Crowley FRCPI,
Department of Obstetrics & Gynaecology,
Coombe Women's Hospital,
DUBLIN 8,
EIRE

Lois Reynolds
l.reynolds@ucl.ac.uk
www.ucl.ac.uk/histmed
Tel: *020 7679 8123*
Fax: *020 7679 8192*

9 June, 2005

Dear Professor Crowley,

Witness Seminar: Prenatal Corticosteroids, 15 June 2004

I hope you have received the draft copy of the transcript on *'Prenatal Corticosteroids for reducing Morbidity and Mortality'*, to which you contributed.

We have yet to receive any comments or corrections, so we are enclosing a copy of the original letter of 7 December 2004, the pages with your contribution and a second copyright assignment form (plus one for your records).

Your corrections along with any correspondence will be deposited in Archives and Manuscripts, Wellcome Library, along with the tapes from the meeting.

I would be grateful if you could return your corrections within **two weeks**, by **25 June 2005**.

Any further delay could compromise the planned publication date of November 2005. Earlier volumes are freely available at: www.ucl.ac.uk/histmed/witnesses.html

If you think I could answer any questions, please contact me by telephone on 020 7679 8123, by fax on 020 7679 8193 or by e-mail at *l.reynolds@ucl.ac.uk*

Yours sincerely,

Mrs Lois Reynolds
Research Assistant to Dr Tilli Tansey
cc: pcrowley@coombe.ie
enc: Crowley pages, 2 x copyright assignment form, original letter 7/12/04

CORTICO
IS JULY 05
CROWLEY

Lois Reynolds

From: Iain Chalmers [IChalmers@jameslindlibrary.org]
Sent: 15 July 2005 08:21
To: ucgarey@ucl.ac.uk
Cc: patc@indigo.ie
Subject: RE: Witness Seminar: Corticosteroids : Patricia Crowley

Dear Lois

I've just spoken to Professor Crowley. Please would you send the transcript electronically to her at patc@indigo.ie today, and she will get back to you promptly with suggested edits.

Best wishes, Iain C

-----Original Message-----
From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: 14 July 2005 13:46
To: Iain Chalmers
Subject: Witness Seminar: Corticosteroids : Patricia Crowley

Dear Sir Iain,

I have been unable to contact Professor Crowley at the address and email below. I would be grateful for any other contact that you could suggest.

We would like to send the final proof out this summer, but are reluctant to do so with a very large part of the transcript in its original state.

Best wishes from Lois Reynolds

0-0-0-0-0

Professor Patricia Crowley FRCPI, Department of Obstetrics & Gynaecology, Coombe Women's Hospital, Dublin 8, EIRE

email: pcrowley@coombe.ie

0-0-0-0-0

Mrs Lois Reynolds
Research Assistant to Dr Tilli Tansey
History of Twentieth Century Medicine Group
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210 Euston Road,
LONDON
NW1 BE

Tel: 020 7679 8123
email: l.reynolds@ucl.ac.uk
Fax: 020 7679 8192
www.ucl.ac.uk/histmed/witnesses.html

--
Virus scanned by Lumison.

Lois Reynolds

From: Lois Reynolds [ucgarey@ucl.ac.uk]
Sent: 01 August 2005 13:08
To: Patricia Crowley
Subject: RE: Witness Seminar: Corticosteroids : corrections needed

Crowley-cprtf orm-9605.doc

Many thanks, Professor Crowley, for your corrections. May I send a corrected version this afternoon by email, so that you are happy with the version that is distributed for return by the first week in September?

And, we would be grateful if you could sign the copyright assignment form and return it by post.

Best wishes from Lois

-----Original Message-----
From: Patricia Crowley [mailto:patc@indigo.ie]
Sent: 31 July 2005 19:44
To: ucgarey@ucl.ac.uk
Subject: RE: Witness Seminar: Corticosteroids : corrections needed

Dear Mrs Reynolds,

Please forgive me for my delaying your work on the Witness Seminar. I attach a corrected version of my contribution. I am leaving for annual leave on Saturday August 6th. If there are amendments you would like me to make before that date please E-mail me and in addition telephone me on 00353 872547633. Please telephone me, using this number also, when you are sending the proofs. Please convey to Dr. Tansey my apologies for delaying matters. It was a poor response to the great pleasure I derived from being involved with the Witness Seminar and to the events it records.

-----Original Message-----
From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: 15 July 2005 11:31
To: patc@indigo.ie
Subject: Witness Seminar: Corticosteroids : corrections needed

Dear Professor Crowley,

We are grateful to Sir Iain Chalmers for sharing this email contact and hope all is well with you.

Attached are your pages, the original letter sent in December 2004, the recent reminder letter and the copyright assignment form which gives us your permission to publish your contribution.

I would be grateful for your comments, corrections, and a 2-3 sentence biographical note (sample for style at the end of your pages), which can be sent by email. Please sign the copyright assignment form and post it to the address below.

With some luck a final proof copy will be sent to you in August or early

September for return within 5 days, if we are to meet our publication deadline in November.

Best wishes from Lois Reynolds, co-editor with Tilli Tansey

Mrs Lois Reynolds
Research Assistant to Dr Tilli Tansey
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at UCL
210 Euston Road,
LONDON
NW1 BE

Tel: 020 7679 8123
email: l.reynolds@ucl.ac.uk
Fax: 020 7679 8192
www.ucl.ac.uk/histmed/witnesses.html

engage in evidence-based practice. I spend a lot of my time at the moment with professors of education who don't believe in systematic reviews of the evidence. This is about the role of the expert, and the relationship between research, evidence and policy across a lot of different sectors.

Crowley: As an obstetric senior registrar in 1985, I took over the care of a woman who was having an antepartum haemorrhage at 37 weeks gestation. We thought she was 37 weeks because of an error in estimating the dates made earlier in the pregnancy. Because of continuing antepartum haemorrhage I induced labour following consultation with a supervising consultant. She had not had antenatal steroids. She was, in fact, only 33 weeks gestation and the baby went on to develop severe RDS and after prolonged ventilation survived with severe cerebral palsy. His mother sued the hospital, my consultant colleague and myself. The patient was awarded Euros 4000 million compensation in an out-of-court settlement because I had failed to give her antenatal steroids. The decision by the protection society and the legal team was that whereas other obstetricians might be able to defend themselves against not giving antenatal steroids in 1985, the papers I had published demonstrating the evidence in favour of antenatal steroids prior to 1985 rendered my failure to prescribe antenatal steroids indefensible. So a very disabled 20-year-old man and his parents have suffered a lot as a result. This medico–legal event contributed a further chapter to my 30-year personal involvement with the antenatal steroid story.[172]

Hey: One of the good things that came out of the book, *Effective Care in Pregnancy and Childbirth*, was a version which has been widely read by parents, wasn't it?[173] Not many other branches of medicine have pursued it through to that point yet, have they?

---

[172]

[173] Dr Edmund Hey wrote: 'The first edition of *A Guide to Effective Care in Pregnancy and Childbirth* was published in 1989 [Enkin *et al.* (1989)]. There have been two further

Lois Reynolds

To: Patricia Crowley
Subject: RE: Witness Seminar: Corticosteroids : no attachment received 6/9/05

no attachment found 27/9/05

Thanks, Patricia. Best wishes from Lois

-----Original Message-----
From: Patricia Crowley [mailto:patc@indigo.ie]
Sent: 11 September 2005 17:09
To: ucgarey@ucl.ac.uk
Subject: RE: Witness Seminar: Corticosteroids : no attachment received 6/9/05

Attached tables with amendments requested

-----Original Message-----
From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: 06 September 2005 16:38
To: Patricia Crowley
Subject: RE: Witness Seminar: Corticosteroids : no attachment received 6/9/05

Dear Patricia, no attachment. Looking forward to seeing your corrections. May I get back to you in the next week or so with any queries? Best wishes from Lois

-----Original Message-----
From: Patricia Crowley [mailto:patc@indigo.ie]
Sent: 05 September 2005 20:21
To: ucgarey@ucl.ac.uk
Subject: RE: Witness Seminar: Corticosteroids : corrections needed

Lois,
Attached amendments for page numbers and titles highlighted in yellow. I hope these are helpful.

-----Original Message-----
From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: 03 August 2005 11:49
To: Patricia Crowley
Subject: RE: Witness Seminar: Corticosteroids : corrections needed

Thank you, Dr Crowley, for your corrections.

Attached is a WORD document of the illustration distributed at the meeting.
I would be grateful if you could add the page numbers and titles highlighted in yellow. I am particularly concerned about the correct citation of the 2004 Cochrane Library reference.

I would be happy to send the final proof copy of this transcript to

another
address, other than the following, if you could let me know before Saturday:

Professor Patricia Crowley FRCPI,Department of Obstetrics & Gynaecology, Coombe Women's Hospital, DUBLIN 8, EIRE

As you will know from your own experience, final proofs need a very close
reading, particularly of the references. And it is vital that we receive your corrections during the first week in September. I hope it will be possible for me to contact you again by email with any other queries that arise in September.

Have a lovely holiday.

Best wishes from Lois

-----Original Message-----
From: Patricia Crowley [mailto:patc@indigo.ie]
Sent: 31 July 2005 19:44
To: ucgarey@ucl.ac.uk
Subject: RE: Witness Seminar: Corticosteroids : corrections needed

Dear Mrs Reynolds,
Please forgive me for my delaying your work on the Witness Seminar. I attach a corrected version of my contribution. I am leaving for annual leave on Saturday August 6th. If there are amendments you would like me to make before that date please E-mail me and in addition telephone me on 00353 872547633. Please telephone me, using this number also, when you are sending the proofs. Please convey to Dr. Tansey my apologies for delaying matters. It was a poor response to the great pleasure I derived from being involved with the Witness Seminar and to the events it records.

-----Original Message-----
From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: 15 July 2005 11:31
To: patc@indigo.ie
Subject: Witness Seminar: Corticosteroids : corrections needed

Dear Professor Crowley,
We are grateful to Sir Iain Chalmers for sharing this email contact and
hope all is well with you.
Attached are your pages, the original letter sent in December 2004, the
recent reminder letter and the copyright assignment form which gives us your permission to publish your contribution.
I would be grateful for your comments, corrections, and a 2-3 sentence
biographical note (sample for style at the end of your pages), which can be sent by email. Please sign the copyright assignment form and post it to the address below.
With some luck a final proof copy will be sent to you in August or early

September for return within 5 days, if we are to meet our publication deadline in November.

Best wishes from Lois Reynolds, co-editor with Tilli Tansey

Mrs Lois Reynolds
Research Assistant to Dr Tilli Tansey
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www.ucl.ac.uk/histmed/witnesses.html

The Wellcome Trust Centre is supported by the Wellcome Trust, a registered charity, no. 210183.

CROWLEY.

Final Amendments to Prenatal Corticosteroids for Reducing Morbidity and Mortality in Preterm Birth.

Page 27 – no change

Page 28. Paragraph 2, Line 12. Obstetricians were obsessed with trying to stop preterm labour rather than *with* trying to improve the outcome ……
I think with is better than "on"

Page 29 Footnote reference 39
Howie RN, Liggins GC. (1978) Clinical Trial of Antepartum Betamethasone Therapy for Prevention of Respiratory Distress in Preterm Infants. In: Anderson A, Beard R, Brudenell JM, DunnPM (eds) *Preterm Labour*: Proceedings of the Fifth Study Group of the Royal College of Obstetricians and Gynaecologists : Royal College of Obstetricians and Gynaecologists. London pp 281-289..

Page 29.Line 9. Delete "And". Should read "I based the paper ….

Page 30. No changes.

Page 31. No changes

Page 32. Paragraph 3. Line 4.. Amend to " Work from Melbourne in the 1970s…" delete Bill Kitchen.

Reference Number 47 should read
Crowley P, Chalmers I, Keirse M (1990) The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials. British Journal of Obstetrics and Gynaecology 97,11-25.

Reference 48.
Doyle L W, Kitchen W H, Ford G W, Rickards A L, Lissenden J V, Ryan M M. (1986) Effects of antenatal steroid therapy on mortality and morbidity in very low birth weight infants. *Journal of Paediatrics* **108**: 287–92.

Page 33. Reference 50.
Crowley PA (1995) Antenatal corticosteroid therapy: a meta-analysis of the randomised trials, 1972 to 1994. American Journal of Obstetrics and Gynaecology 173:332-335

Page 34… No change.

Page 39. Paragraph 3. Should read "systematic reviews" not systematic trials. Typo in systematic.

Page 43. Second paragraph. Reference to excessive performance of subgroup analyses refers to Roberton reference already expanded upon on page 31 and reference footnoted as Reference no 45. The counter-argument appears in all the systematic reviews already

Roberton (1982)?

based on document dated 5/8/05.

Rec'd 27/10/05

corrected 27/10/05.

cited e.g. Oxford database 1987; Crowley et al 1990; Crowley 1995; Cochrane Review 2005.

Page 44. No change.

Page 89. No change.

Page 91. Paragraph entitled Crowley.Line 9. Should read 4 million euro not 4,000 million euros.

Footnote 159 In relation to date –child born in 1985. Legal settlement of 4 million in 2003.

Page 113. Biographical note ….. Senior Lecturer at the Department of Obstetrics and Gynaecology, Trinity College Dublin since 1990.

PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY

The transcript of a Witness Seminar held by the Wellcome Trust Centre for the History of Medicine at UCL, London, on 15 June 2004

Edited by L A Reynolds and E M Tansey

Dr Patricia Crowley: I first heard about antenatal corticosteroids in an undergraduate lecture in 1974. The possibility of preventing RDS made an immense impact on me because the first baby I delivered as an undergraduate died in the neonatal period from RDS, despite weighing seven pounds and being born at 36 weeks. So the scene was set for a life-long interest in this topic. Later, in 1977, as a senior house officer in neonatal paediatrics, I attended a lecture on fetal lung maturation given by Professor Mel Avery, who was an invited lecturer at the Irish Perinatal Society. At a time when young female medical graduates had few role models, an innovative paper delivered by an attractive woman made an enormous impression, especially as I was continuing to see premature babies die on a regular basis from RDS.

At that time I was working in the National Maternity Hospital, Dublin, which fostered a culture of nihilism towards most medical interventions, with the exception of those ordained by institutional policy. I encountered a woman whose previous baby had died from RDS, and together with a paediatric colleague, approached the Master (Clinical Director) of the hospital to obtain permission to prescribe antenatal corticosteroids for this patient. That was the first and only time in a two-year spell in obstetrics and paediatrics between 1976 and 1978 that I was allowed to prescribe antenatal steroids.

I then went to work in the Hammersmith Hospital in London and in 1978 attended a meeting at the Royal College of Obstetricians and Gynaecologists (RCOG) marking the publication of the proceedings of the 1977 RCOG Preterm Labour Study Group. Ross Howie had attended this meeting in 1977, and presented a paper jointly authored with Mont Liggins on the outcome of 1068 women and their babies who had been enrolled in randomized trials of antenatal corticosteroid therapy. This showed a massive reduction in neonatal mortality in those babies who were exposed *in utero* to antenatal steroids.[1] The Proceedings of that Preterm Labour Study Group contained 14 papers on tocolysis and only two papers about fetal lung maturation – a clear indication of where the emphasis of British obstetrics lay at that time when it came to preterm labour. Obstetricians were obsessed with trying to stop preterm labour rather than on trying to improve the outcome for the premature baby by accelerating lung maturation. Despite a dearth of objective evidence of efficacy, a variety of betasympathomimetic drugs were being actively

[1] Howie and Liggins (1978).

promoted by the pharmaceutical industry at this time, whereas no pharmaceutical company was promoting the use of antenatal steroids.

In 1980 at the Hammersmith Hospital, London, Professor Denis Hawkins founded the *Journal of Obstetrics and Gynaecology*. He received a paper from Ben Sachs, a British obstetrician working in the US, which reviewed the adverse effects of antenatal steroids and the lack of evidence to support their efficacy.[2] He challenged me to write an opposing view to this manuscript. This led to a paper written in 1980 and published in 1981, entitled 'Corticosteroids in pregnancy: the benefits outweigh the costs'[3]. I was either lucky or lazy, because I decided to ignore observational evidence. Although I had never been taught that the randomized controlled trial was the best form of evidence, instinct led me in that direction. My literature search yielded four randomized controlled trials of antenatal steroids. And I based the paper on two tables derived from amalgamating the results of the four trials, showing substantial reductions in neonatal mortality and morbidity in babies whose mothers were randomized to receive antenatal steroids. [See Tables 1 and 2.]

	Maturity (weeks)	Betamethasone-treated group (%)	Control group (%)	Difference
Liggins and Howie (1972)	24–37	4	24	$P < 0.002$
Block *et al.* (1977)	<37	10	27	$P < 0.05$
Papageorgiou *et al.* (1979)	25–34	18	58	$P < 0.005$
Tauesch *et al.* (1979)	<36	13	30	$P = 0.085$

Table 1. Incidence of respiratory distress syndrome as percentages of live preterm births.
Data taken from Crowley (1981): 148.

	Betamethasone-treated group (%)	Control group (%)	Difference
Liggins and Howie (1972)	4	24	$P < 0.002$
Block *et al.* (1977)	10	27	$P < 0.05$
Papageorgiou *et al.* (1979)	18	58	$P < 0.005$

Table 2. Perinatal mortality rates as percentages of preterm births.
Data taken from Crowley (1981): 148.

By the time this paper was published in 1981 I had started a nine-month attachment at the National Perinatal Epidemiology Unit (NPEU), which was one of the most rewarding periods of my professional life. Anne Anderson and Iain Chalmers read the paper and invited me to contribute a chapter on antenatal steroids to a book that they were planning on *Effective Care in Labour and Delivery*. This was intended to follow *Effectiveness and Satisfaction in Antenatal Care*.[4] I started work on a chapter on fetal lung maturation, examining the evidence in relation to antenatal corticosteroids and any other agents that aimed to accelerate pulmonary maturation.

Progress on this proposed book was delayed by the illness and eventual death of Anne Anderson. It was eventually subsumed into a much more ambitious venture, *Effective*

[2] Sachs (1981).

[3] Crowley (1981).

[4] Enkin and Chalmers (eds) (1982).

Care in Pregnancy and Childbirth.[5] Meanwhile, led by Iain Chalmers, a group of individuals based at or associated with the National Perinatal Epidemiology Unit, became involved with the development of the Oxford Database of Perinatal Trials, which aimed to identify, assemble and analyse all published and unpublished randomized controlled trials available in the world literature in perinatal medicine.

I left Oxford in 1981 and returned to Dublin to continue to train as an obstetrician but maintained my contact with the NPEU. My associates working with the Oxford Database regularly alerted me to new trials that had been uncovered by enthusiasts who had searched the literature to find randomized trials. The next three years saw the publication of follow-up data from the Auckland trials and of the results of the US NIH Collaborative Group on Antenatal Steroid Therapy study.[6] With hindsight, we could ask whether the Collaborative Group trial should ever have taken place, because at the time when recruitment was taking place for that trial there was already substantial evidence in the literature that antenatal steroids were effective and safe. If we look at the 1000 or so babies who received antenatal steroids in the randomized trials prior to 1980, and the 1000 babies who received placebo in these trials, 130 of the babies who received placebo died, compared with 70 of the babies who received antenatal steroids. Were those who were recruiting participants for the NIH Collaborative Group trials unaware of these results? Had clinicians or parents been aware of these results, it would have been difficult to persuade anyone to be randomized to placebo in the late 1970s or early 1980s.

As the 1980s progressed, I regularly updated my collection of randomized trials. Because of a series of subgroup analyses emerging from the US NIH Collaborative Group trials, I became interested in sub-group analysis of the outcomes of the accumulated trials. Commentators on the NIH trial reported that antenatal steroids were effective mainly in babies of between 32 and 34 weeks, and 'worked' in black females but not in white males.[7] I went back to the collection of trials that I had accumulated and looked at what happened to white males in Auckland and found they benefited from antenatal steroids. This was how many of the sub-group analyses produced in the original systematic review of randomized trials came into being. It was driven by a need to refute a number of reviews questioning the efficacy of antenatal steroids based on these sub-group analyses, principally from the NIH Collaborative Group study.

Some form of systematic review of antenatal steroids was part of my life in various ways throughout the early 1980s. The proceedings from a conference I attended in Italy in 1984 show that by then I was looking at the outcome of seven trials, loosely synthesising the outcomes.[8] In 1987 to 1988 the technology became available at the NPEU to produce a meta-analysis with electronically entered data, and to generate results in the form of Odds Ratios with confidence intervals. The review of antenatal steroids became

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[5] Chalmers *et al.* (eds) (1989).

[6] Collaborative Group on Antenatal Steroid Therapy (1981).

[7] Roberton (1982).

[8] Crowley (1986).

the first to be entered to the Oxford Database of Perinatal Trials. This was a very exciting time, when, after years of collecting data, I saw graphic evidence of the efficacy of antenatal steroids in preterm babies in general and in all relevant sub-groups.

By 1989, when the results of the antenatal corticosteroid review were available in an attractive, accessible electronic format on the Oxford Database of Perinatal Trials and on paper in the book *Effective Care in Pregnancy and Childbirth*, I thought that this information was accessible to obstetricians around the world, and believed that no further publications were necessary to promote the use of antenatal corticosteroids. However, I was eventually persuaded by Iain Chalmers to publish a paper version of this systematic review in the *British Journal of Obstetrics and Gynaecology*.[9]

Looking at practice throughout the world with respect to antenatal steroid use, it is only after 1990 that we can see any more than 20 per cent of preterm babies being exposed to antenatal steroids in any country, with the exception of Australia and New Zealand. Work from Bill Kitchen in Melbourne in the 1970s, showed 45 per cent of Melbourne babies in the 1970s were treated with antenatal steroids prior to delivery.[10] Elsewhere around the world, it fell often under 10 per cent and never higher than 20 per cent, up to 1990. So the publication of this paper in the *British Journal of Obstetrics and Gynaecology* was a landmark in terms of improving the use of antenatal [?prenatal?] steroids.[11]

In 1994 the NIH Consensus Conference on antenatal steroids took place.[12] At that meeting I contributed an updated version of the systematic view of antenatal steroids,[13] derived mainly from the electronic review published on what was by then the *Cochrane Pregnancy and Childbirth Database of Perinatal Trials*.[14] The rest of that three-day meeting was taken up with many observational studies, and laboratory-based papers on

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[9] Crowley *et al.* (1990).

[10] [Which reference?? Text says 1970s.....]Doyle L W, Kitchen W H, Ford G W, Rickards A L, Lissenden J V, Ryan M M. (1986) Effects of antenatal steroid therapy on mortality and morbidity in very low birth weight infants. *Journal of Paediatrics* **108**: 287–92. OR these two from the Australian Wit Sem: Kitchen W H, Ryan M M, Rickards A *et al.* (1978) A longitudinal study of very low-birthweight infants I: Study design and mortality rates. *Developmental Medicine and Child Neurology* 20, 605–18. Kitchen W H, Rickards A, Ryan M M *et al.* (1979) A longitudinal study of very low-birthweight infants II: Results of controlled trial of intensive care and incidence of handicaps. *Developmental Medicine and Child Neurology* **21**: 582-589. For further details, see www.cshs.unimelb.edu.au/programs/jnmhu/witness/001.html (visited 2 August 2005).

[11] Can you suggest a more recent reference here?

[12] National Institutes of Health (NIH) (1994). Their recommendation was to give a single course of corticosteroids – two doses of 12mg of betamethasone given intramuscularly 24 hours apart or four doses of 6mg of dexamethasone given intramuscularly 12 hours apart – to all pregnant women between 24 and 34 weeks gestation considered to be at risk, clinically, of preterm delivery within 7 days. Freely available at http://consensus.nih.gov/1994/1994AntenatalSteroidPerinatal095html.htm (visited 28 September 2005). See also Consensus Conference (1995).

[13] Crowley (1995). Fifteen trials listed in descending order of quality presented at the NIH Consensus Development Conference in Bethesda, MD, on 28 February 1994.

[14] The first systematic review by Crowley appeared on the Oxford Database of Perinatal Trials in 1987. The 1996 version appears as an example of a Cochrane Review at www.cochrane.org/reviews/exreview/htm (visited 2 August 2005). See also Figure 6.

antenatal steroids and following the three-day meeting a strong recommendation was released, urging obstetricians in the US to use antenatal [?prenatal?] steroids.

In 1996 I was invited by the Royal College of Obstetricians and Gynaecologists to update a guideline on the use of antenatal steroids issued in 1992.[15] The revised guideline, based on the systematic review published in the Cochrane Library, strengthened the recommendation from the RCOG on antenatal steroids use. By the late 1990s, 70 per cent of preterm babies delivered in the UK were being treated [??whose mothers had been treated??] with antenatal [?prenatal?] steroids prior to delivery.

Within a year or two of finally adopting the evidence-based practice of prescribing a single course of antenatal steroids to women at risk of delivering a preterm infant, obstetricians started to prescribe repeated courses of antenatal [?prenatal?] steroids. The practice of repeated courses of antenatal [?prenatal?] steroids to women who remain undelivered a week or more following the original treatment crept in rapidly, without any evidence to support its safety or efficacy. All the evidence from randomized trials related to a single course of antenatal [?prenatal?] corticosteroid therapy.

[Figure 4 here: Caption reads: Meta-analyses, 1992–2004.

1. 7 trials, Cochrane logo, 1992;

2. 12 trials, Crowley (1989);

3. 15 trials, Sinclair (1995);

4. Cumulative meta-analysis of first 15 trials, Sinclair (1995);

5. 18 trials, Cochrane Library (2004).

This widespread practice, unsupported by any evidence, generated the need for a new round of randomized trials to evaluate the immediate and long-term benefits and hazards of a single course, versus repeated courses, of antenatal [?prenatal?] steroids. These trials are currently recruiting. Had the publication of the Auckland trial in 1972 been followed rapidly by a large multicentre trial and by the subsequent use of a single course of antenatal [?prenatal?] steroids as the standard of care, trials of single versus repeat courses of antenatal [?prenatal?] l steroids would have taken place in the 1980s. So, largely due to a collective professional failure to disseminate and implement evidence concerning an effective intervention, progress in the area remains about 20 years behind where it should be.

...

Crowley: Through all the systematic reviews of the trials we have kept an eye on intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL). There is good evidence that these adverse outcomes are reduced by antenatal steroids across the gestational ages. The use of early postnatal steroids is associated with an increased risk of adverse outcome. Antenatal steroids are protective in terms of neonatal neurology,

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[15] See note **Error! Bookmark not defined.**.

whether you look at the brain at autopsy or with imaging techniques for PVL. Would you agree with that, Jane?

...

Crowley: I think the results of the US Collaborative Group trial set things back, because this was the first of the randomized trials published that didn't show any difference in neonatal mortality, even though it showed a difference in respiratory distress and in particular the duration and the cost of neonatal care. This was the first trial that looked at economic outcomes. But nonetheless, the lack of difference in neonatal mortality seemed to get a lot of press and then the excessive performance of sub-group analyses was given undue emphasis, even though these sub-groups had not been specified at the start of the trial. They were produced following data-dredging after the trial had concluded, and these were emphasized, for instance, in that editorial by Cliff Roberton.[16] You referred to the survey of Members and Fellows of the Royal College of Obstetricians and Gynaecologists, which asked obstetricians about their practice and what they said they did, which is not the same as what we actually do.[17] While 44 per cent of obstetricians surveyed in 1979 said that they used antenatal corticosteroids 'often', only 12 per cent of preterm babies recruited to the UK Ten Centre Study of artificial surfactant had been exposed to steroids antenatally.[18]

...

Crowley: Could I remind you that in the Auckland trial a lot more babies died in the placebo group, and therefore one might have expected an increased incidence of adverse neurological outcome in the survivors from the steroid-treated group compared with the control group. These survivors have now been assessed at 30 years of age, and if there's no difference between the two groups at age 30, it's unlikely that there is any hazard associated with a single dose of antenatal [?prenatal?] steroids.

...

Crowley: Probably a very important one is the reduction in the risk of IVH and that's a particular benefit for the most premature babies. Also a reduced number of days on mechanical ventilation for babies who do get RDS.

...

---

[16] See Roberton (1982). Dr Crowley, could you elaborate on the sub-group analysis? Is there a table that could illustrate this point?

[17] Lewis *et al.* (1980).

[18] Lewis *et al.* (1980); Ten Centre Study Group (1987).

Crowley: As an obstetric senior registrar in 1985, I took over the care of a woman who was having an antepartum haemorrhage at 37 weeks gestation. We thought she was 37 weeks because of an error in estimating the dates made earlier in the pregnancy. Because of continuing antepartum haemorrhage I induced labour following consultation with a supervising consultant. She had not had antenatal steroids. She was, in fact, only 33 weeks gestation and the baby went on to develop severe RDS and after prolonged ventilation survived with severe cerebral palsy. His mother sued the hospital, my consultant colleague and myself. The patient was awarded Euros 4000 million compensation in an out-of-court settlement because I had failed to give her antenatal steroids. The decision by the protection society and the legal team was that whereas other obstetricians might be able to defend themselves against not giving antenatal steroids in 1985, the papers I had published demonstrating the evidence in favour of antenatal steroids prior to 1985 rendered my failure to prescribe antenatal steroids indefensible. So a very disabled 20-year-old man and his parents have suffered a lot as a result. This medico–legal event contributed a further chapter to my 30-year personal involvement with the antenatal steroid story.

....

Dr Patricia Crowley
FRCOG FRCPI (b 1951) has been a consultant Obstetrician Gynaecologist at the Coombe Women's Hospital, Dublin, and Senior Lecturer at the Department of Obstetrics and Gynaecology, Trinity College Dublin since 19xx.

Lois Reynolds

From: Patricia Crowley [patc@indigo.ie]
Sent: 31 October 2005 17:07
To: ucgarey@ucl.ac.uk
Subject: RE: Witness Seminar :outstanding queries : 31 Oct 05 : urgent

OK 31/10/05

Lois,
The reference for the paper arising out of the 1984 conference in Italy is as follows
Crowley P. Enhancement of fetal lung maturity with corticosteroids. In Selected Topics in Perinatal Medicine. Edited by Ermelando V Cosmi, Gina Carlo Di Renzo. CIC Edizioni Internazionali, Roma pages 143-148. I have the book in my hand and cannot find the year of publication mentioned anywhere. However, I have noted elsewhere that this was published in 1986.

The amendment to page 32 is welcome, although I would prefer "delivered ***to*** mothers" rather than ***"from*** mothers".
(1) page 32: Work from Melbourne in the 1970s, showed 45 per cent of Melbourne babies in the 1970s [??were delivered from mothers who had been treated?] were treated with antenatal steroids prior to delivery.[1][1]

From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: 31 October 2005 13:47
To: patc@indigo.ie
Subject: FW: Witness Seminar :outstanding queries : 31 Oct 05 : urgent

Dear Patricia,
Hope you received the email below, sent on 27 October. I need your reply today, if possible.
Also, you mention your article of 1986, which I do not have in the references. The context follows.
Best wishes from Lois

0-0-0-0-0
Crowley: .....The proceedings from a conference I attended in Italy in 1984 show that by then I was looking at the outcome of seven trials, loosely synthesizsing the outcomes.[2][1]

-----Original Message-----
From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: 27 October 2005 13:38
To: Patricia Crowley
Subject: Witness Seminar :outstanding queries : 31 Oct 05

Dear Patricia,

Thank you for your corrections. May I ask the following?
(1) page 32: Work from Melbourne in the 1970s, showed 45 per cent of Melbourne babies in the 1970s [??were delivered from mothers who had been treated?] were treated with antenatal steroids prior to delivery.[3][1]

---

(2) Attached is the copyright assignment form, which gives us permission to publish your contribution, which I would be grateful if you could print out, sign and return to me at:

Mrs Lois Reynolds,
Wellcome Trust Centre for the History of Medicine at UCL,
210 Euston Road,
LONDON, NW1 2BE.

Many thanks for your help. Best wishes from Lois

-----Original Message-----
From: Patricia Crowley [mailto:patc@indigo.ie]
Sent: 26 October 2005 21:23
To: l.reynolds@ucl.ac.uk
Subject: Final Amendments to Witness Seminar

Dear Mrs Reynolds. Please forgive me for all the delays that I have caused you in this project to date. Call me on 00-353-872547633 if any outstanding queries remain.

---

[1][1] Doyle *et al.* (1986). For a discussion on the evolution of paediatrics at the University of Melbourne Department of Paediatrics at the Royal Children's Hospital 1959–2003, see www.cshs.unimelb.edu.au/programs/jnmhu/witness/001.html (visited 2 August 2005).

Tilli asks whether the bracketed material in red above is clearer?

[2][1] Crowley (1986).

0-0-0-0-0

[3][1] Doyle *et al.* (1986). For a discussion on the evolution of paediatrics at the University of Melbourne Department of Paediatrics at the Royal Children's Hospital 1959–2003, see www.cshs.unimelb.edu.au/programs/jnmhu/witness/001.html (visited 2 August 2005).

Tilli asks whether the bracketed material in red above is clearer?

ok 1/11/05.

Lois Reynolds

From: Patricia Crowley [patc@indigo.ie]
Sent: 31 October 2005 17:16
To: ucgarey@ucl.ac.uk
Subject: RE: Witness Seminar: Prenatal corticosteroids : Mel Avery

Lois,
I leave that judgement in your hands. My very clear memory of her lecture on antenatal steroids in Dublin 1977 is of a smiling woman with a great enthusiasm for her subject, and enthusiasm is certainly attractive. I agree that the photograph proves the point but she was even better "live".

----Original Message-----
From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: 26 October 2005 19:18
To: patc@indigo.ie
Subject: Witness Seminar: Prenatal corticosteroids : Mel Avery

Dear Patricia,
Attached is a photograph of Mel Avery in 1965. You remarked at the meeting
that when you first heard a lecture by her you were surprised that such an attractive woman was on the podium. I believe that we altered that part of your contribution. May I reinstate it? This photograph proves your point, which is one that is rarely heard.
Best wishes from Lois

Mrs Lois Reynolds
Research Assistant to Dr Tilli Tansey
History of Twentieth Century Medicine Group
Wellcome Trust Centre for the History of Medicine
at UCL
210 Euston Road,
LONDON
NW1 BE

Tel: 020 7679 8123
email: l.reynolds@ucl.ac.uk
Fax: 020 7679 8192
www.ucl.ac.uk/histmed

FN 1+1

Lois Reynolds

Checked 1 NOV 05

From: Denise Atherton [datherto@liverpool.ac.uk]
Sent: 01 November 2005 09:15
To: ucgarey@ucl.ac.uk
Cc: S.L.Henderson@liverpool.ac.uk
Subject: Re: FW: Witness Seminar: Prenatal Corticosteroids, urgent query

Dear Lois
Thank you for your message. I have been in touch with the author who is updating this review, who confirms that the contribution and footnote are correct.
with best wishes,
Denise

--On 31 October 2005 12:30 +0000 Lois Reynolds <ucgarey@ucl.ac.uk> wrote:

> Dear Denise,
> I hope you will be able to assist with my question to Sonja Henderson, as
> my deadline is fast approaching. Best wishes from Lois Reynolds
>
> -----Original Message-----
> From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
> Sent: 31 October 2005 12:26
> To: s.l.henderson@liverpool.ac.uk
> Subject: Witness Seminar: Prenatal Corticosteroids, urgent query
>
>
> Dear Mrs Henderson, Review Group Coordinator,
> I would be grateful if you could let me know whether the following
> contribution and accompanying footnote are correct. The text for this
> volume of the Wellcome Witnesses to Twentieth Century Medicine, vol. 25,
> 'Prenatal corticosteroids for reducing morbidity and mortality after
> preterm birth' is going to the designer tomorrow, for publication before
> Christmas. The original meeting was held on 15 June 2004.
> Best wishes from Lois Reynolds
>
> 0--0-0-0
>
> Professor Jane Harding (Auckland, NZ): There have been at least four
> trials in the 1990s and I am sure Dr Crowley will talk about this. But
> the new Cochrane Review, which is in the process of being produced, will
> show clearly that the benefit is still there in the surfactant era, in the
> ventilator era and in the four randomized placebo control trials done in
> the 1990s.
>
> FN. See, for example: Carlan et al. (1991); Garite et al. (1992); Kari et
> al. (1994); Botet et al. (1994); Lewis et al. (1996); Silver et al.
> (1996); Amorim et al. (1999); Pattinson et al. (1999); Qublan et al.
> (2001) Fekih et al. (2002). The new Cochrane Review will not be available
> until 2006.
>
> 0-0-0-0
>
>

> Mrs Lois Reynolds
> Research Assistant to Dr Tilli Tansey
> History of Twentieth Century Medicine Group
> Wellcome Trust Centre for the History of Medicine
> at UCL
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>
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> www.ucl.ac.uk/histmed
>
> The Wellcome Trust Centre is supported by the Wellcome Trust, a registered
> charity, no. 210183.
>
>

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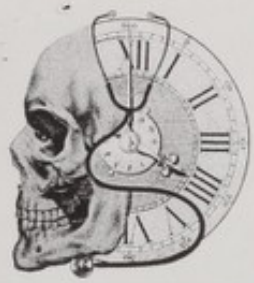
Email: datherto@liverpool.ac.uk



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UCL

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Fax: +44 (0) 20 7679 8193

Dr Stuart Dalziel
Research Fellow
Clinical Trials Research Unit
University of Auckland
Private Bag 92019
Auckland
NEW ZEALAND

20 April 2004

Fax: 00 649 367 1710

Dear Dr Dalziel

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004 2pm-6pm

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is organising a Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15th June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1. Dr Edmund Hey has kindly agreed to chair the meeting and Sir Iain Chalmers is assisting us in the organisation.

These seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history. I attach a copy of the introduction to the first volume of our published transcripts, which will tell you a little more about these seminars, and lists our recent publications to illustrate the range of topics we cover. I also attach, for your information, a publicity flyer for this meeting and have sent you a complimentary copy of Volume 1 of our Witness Seminar series in the post.

Continued/... Page 2

The Wellcome Trust Centre for the History of Medicine at University College London is funded by the Wellcome Trust, which is a registered charity, no. 210183. Histmed logo images courtesy *Wellcome Library*, London.

As one of the members of the team who are working on the long-term follow up of the patients from the seminal Liggins and Howie trial Sir Iain Chalmers and Dr Edmund Hey feel that your attendance would greatly enhance the success of the meeting. I am writing, therefore, to enquire whether, in principle, you would be able to travel to England to participate as a main witness on Tuesday 15th June 2004. Unfortunately, we do not have the funds to assist with travel from overseas. However, we are able to fund your travel within the UK to and from the meeting and to offer you accommodation for the night of the meeting at the Ibis Hotel London Euston and will reserve an extra night's accommodation if you require it.

It really would be a great opportunity to document this obstetric success story. I look forward to hearing from you and do hope you will be able to accept this invitation.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

atts.

****
*** TX REPORT ***
****

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UCL

Dr Stuart Dalziel
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Tel: +44 (0) 20 7679 8125
Fax: +44 (0) 20 7679 8193

20 April 2004

Fax: 00 649 ~~367 1710~~ 373 7481

Dear Dr Dalziel

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004 2pm-6pm

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is organising a Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15th June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1. Dr Edmund Hey has kindly agreed to chair the meeting and Sir Iain Chalmers is assisting us in the organisation.

These seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 22 April 2004 08:39
To: Carole_Anderson
Cc: Wendy
Subject: RE: Fax to Dr Stuart Dalziel

Importance: High

Thank you for the information and many apologies for using the incorrect fax number. We have amended our records as necessary.
Daphne Christie

-----Original Message-----
From: Carole_Anderson@bnz.co.nz [mailto:Carole_Anderson@bnz.co.nz]
Sent: 22 April 2004 05:33
To: d.christie@ucl.ac.uk
Subject: Fax to Dr Stuart Dalziel

You have tried to send a fax to Dr Stuart Dalziel in New Zealand but the fax number you are using is actually a telephone number at the Bank of New Zealand.
We have looked up the fax number for the University of Auckland and forwarded this on to 373 7481 hoping it will reach Dr Dalziel.
Can you please correct the fax number you are using before sending any further correspondence.
Thank you
Carole Anderson

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 25 May 2004 09:17
To: Stuart Dalziel
Cc: Wendy
Subject: RE: Wellcome Trust Meeting on Perinatal Corticosteroids

Dear Dr Dalziel
Thank you for your e-mail. We are sorry that you are unable to attend the witness seminar on 15 June and are grateful for your offer of help with any additional information we may require about the original trial or the current thirty year follow-up. We will keep you informed about the subsequent witness transcript.
With best wishes
Daphne Christie

-----Original Message-----
From: Stuart Dalziel [mailto:s.dalziel@ctru.auckland.ac.nz]
Sent: 25 May 2004 03:20
To: 'd.christie@ucl.ac.uk'
Cc: Edmund Hey (E-mail) (E-mail)
Subject: Wellcome Trust Meeting on Perinatal Corticosteroids

Dear Dr Christie,

Thank you very much for your invitation to attend the upcoming meeting to be held on perinatal corticosteroids. Unfortunately I am unable to attend as I previously arranged to be in Australia that day for another meeting.

I am more than willing to help in anyway with any additional information you may require about the original trial or the current thirty year follow-up.

I hope the meeting is successful in documenting some of the history surrounding this important paediatric and obstetric development.

Kind regards,

Stuart Dalziel.

Dr Stuart Dalziel

Research Fellow
Clinical Trials Research Unit
University of Auckland
Private Bag 92019
Auckland
Ph: +64 9 3737599 ext. 84722
Fax:+64 9 3671710
e-mail: s.dalziel@ctru.auckland.ac.nz
http://www.ctru.auckland.ac.nz

Dr Daphne Christie

From: Clive Dash [clive.dash@virgin.net]
Sent: 10 January 2005 09:05
To: d.christie@ucl.ac.uk
Subject: Witness Seminar: Prenatal steroids for reducing Morbidity and Mortality

Dear Dr Christie
I was invited to the above Witness Seminar but unfortunately was unable to attend because of prior engagement.
I had several discussions with the late Harold Gamsu in the period before the meeting providing some input to questions raised by Dr Hey as a stimulant for discussion at the meeting.
I have now seen the transcript from Brenda Mullinger and offer a number of observations as the instigator of the UK trial in 1974.
These are attached in a Word document as well as a brief CV of myself should you wish to use it. The paragraphs are referenced to the relevant pages of the transcript. If you wish, you could use them as an Appendix.
Currently, we are in discussion with Peter Brocklehurst in Oxford to try to progress a long-term follow-up on the babies which Harold Gamsu was so keen to do.

Please note a spelling error in my surname on page 38 (Dash not Bash).
If I can be of further help or if you have any questions please feel free to contact me either by e-mail or phone (most days I can be located or a message left on 020 8258 2565.

Kind regards
Clive

2/6/05

Witness Seminar: Prenatal Corticosteroids for reducing Morbidity and Mortality

The UK multicentre study[1] was designed in 1974, largely stimulated by the publication of Liggins & Howie[2] and their prior animal studies. The idea for a UK study was an amalgam of interest from some obstetricians and neonatal paediatricians and from within Medical Dept of Glaxo in the UK because of the organizational link with the antipodes.

Clinicians' views can change during the planning and conduct of long-term studies (about 4 years to plan and complete recruitment and follow-up for the UK study[1]). All clinicians, who were involved in the early planning, recognized that more clinical work was needed to confirm the results from NZ[1]. Everyone involved in the study planning recognized that it was important to have commitment from an obstetrician and paediatrician at each participating hospital*. By the time the study recruitment started (about 1 year later), some of the clinicians did not wish to recruit patients to the study for various reasons, even after Ethics Committee approval. [Pertinent p. 28]
[* Pertinent p. 40]

At the time when Ross Howie presented the results to RCOG in 1977, the UK study was in its recruitment phase. Whether knowledge of the status of the UK study played any part in the cool response of the delegates at the meeting, which Ross sensed, would be speculative. [Pertinent pp.13, 38]

The response by the delegates at the RCOG meeting in 1977 may also have been tempered by the anxiety, certainly among many clinicians with whom I spoke at that time, that the long-term effects might prove to be significant. [Pertinent p. 104]

Because of the Glaxo link, it was well-known in the UK which product had been used in NZ[1]. The NZ product was an ester of betamethasone (acetate), the properties of which caused a slower absorption from the intramusclular site than the very soluble product (phosphate salt) available in the UK. It was estimated that more frequent injections of the soluble product would give a similar bio-availability. The placebo used in the UK was specially prepared for the study by Glaxo and consisted of the vehicle in which the phosphate salt was formulated. Both were clear solutions in identical vials and labeled similarly except for patient numbers assigned randomly. Thus, the blind was preserved.
[Pertinent p.15]

I had the pleasure to meet Mont Liggins on one of his visits to the UK during the early planning of the UK study[1]. As others have said in this Witness Meeting, he was open with his results and encouraging us to do more. [Pertinent pp. 12/14/29/30]

A taxing question in the design and analysis of the UK study was the imprecision in estimating gestational age at the time of recruitment. Maternal dates and obstetrical palpation were the only antenatal assessments available then – so different from the current techniques! The clinicians documented both estimates for the analysis. These were augmented (or confounded) by neonatal assessment[3,4], which was also recorded.

[Pertinent p.21 *this change in clinical assessment is not mentioned in the transcript, but it is important to remind readers of the circumstances that were present when a particular piece of work was undertaken, by contrast to current times*]

In the mid-1970s in the UK, informed consent for clinical trials was generally verbal. It was later that written consent and now written informed consent became part of normal practice. [Pertinent p. 19]

The UK study was being planned at the time of the move from ethanol as a tocolytic to various newly introduced beta-agonists. We decided to use salbutamol, if a tocolytic was clinically necessary, so as to standardize one of the management modalities – and also because salbutamol was developed by Glaxo! [Pertinent p. 30/31]

The UK study[1] finished recruitment in early 1978 and the findings of the initial analysis supported those that had been reported reported elsewhere. These included a mortality benefit especially in infants born before 34 weeks gestation; within 8 days after the mother had entered the study; and if the mother had received at least three injections of betamethasone phosphate (12mg). No new or interesting results were found. Partly because of this, I did not think that publication of the study was a worthwhile priority (insufficiently newsworthy). However, due to the persuasive powers of the late, Harold Gamsu (for whom I have great admiration for his pleasant persistence and continuous striving to fully understand the data) I was persuaded to coordinate a more detailed analysis of the data with other colleagues at Glaxo.

[Pertinent pp. 30, 43]

In the planning of the UK study[1], we discussed whether a single course of betamethasone or, if necessary, repeat courses at weekly intervals was appropriate. We decided on a single course, partly because of worries about safety in the short- and long-term and partly because of the logistics of providing the same blinded medication for each patient.

[Pertinent pp. 35/101]

In the UK study[1], only 20% of the recruited patients delivered between 24 hours and one week after recruitment (25% before 24 hours and 55% after one week).

[Pertinent p. 52]

The retention of clinical trial data in the 1970/80s was poor. This has changed in recent years. When Harold Gamsu persuaded us to do a detailed analysis of the UK study, the computer software had changed and so had most personnel acquainted with the prior system. Luckily, Alex Paton at Glaxo was able to interrogate the database and through her efforts we were able to meet Harold's expectations and answer his critical questions. Also, Harold volunteered to keep safe the original case record forms and other study documentation when Brenda Mullinger and I left Glaxo to pursue other career opportunities. I believe Harold always hoped to trace the babies in adult life to address the question of the long-term safety. It is due to his diligence and enthusiasm that he persuaded us (again, pleasantly) in 2001 to begin the process towards a 30+ years follow-

up. His untimely death occurred in August 2004, soon after this Witness Meeting. We hope to continue this project with the support of NPEU in Oxford provided external support can be mobilized and plan to dedicate any outcomes to his memory.

[Pertinent p. 54/55]

Various preparations of betamethasone are available in different countries. The preparations are all designed to release the active sterol, betamethasone, but at different rates. The soluble phosphate preparation is suitable for intravenous administration, like hydrocortisone, as well as intramuscular injection. The acetate preparation is not suitable for IV use. Some products are a mixture of the acetate and phosphate derivatives (*e.g.*Celestone®, Schering).

[Pertinent p. 105]

In some countries dexamethasone is more readily available than betamethasone and this is why it has featured in some studies. These two steroids are isomers in which the methyl group differs in its orientation (dexamethasone is 9−*alpha*-fluoro 16-*alpha* methyl prednisolone; betamethasone is 9-*alpha*-fluoro 16-*beta* methyl prednisolone)[5]. In the usual pharmacological tests of corticosteroid potency, they are equivalent. In general, the mode of action (pharmacodynamics) seem similar, so they should be therapeutically equivalent.

[Pertinent p. 105]

References

1. Gamsu H R, Mullinger B M, Donnai P, Dash CH. *Br J Obstet Gynaecol* 1989; 96:401-410.
2. Liggins G C, Howie R N. *Pediatrics* 1972; 50: 515-525.
3. Farr V, Mitchell R G, Neligan G A, Parkin J M. *Dev Med Child Neurol* 1966; 8: 507-511.
4. Dubowitz L M, Dubowitz V, Goldberg C. *J Pediatr* 1970; 77: 1-10.
5. Sweetman S C (Ed) Martindale 33rd Ed. Pharmaceutical Press, London 2002; 1063 & 1067.

Dr Clive H Dash

FFPM (b. 1940) instigated and coordinated the UK trial of antenatal steroids in 1974 while working as a clinical research physician for Glaxo in the UK. He graduated from University of Birmingham and did post-graduate obstetrics with Prof Hugh McLaren in Birmingham.
Most of his professional life he has worked in clinical research within the pharmaceutical industry and is now an independent consultant in healthcare and pharmaceutical medicine. A long-term, continuing clinical practice is in Thoracic Medicine.

Josh

See my question on this page.

See my suggestion

Please see page 13, 15, 20, 38, 54, 85, 93 and 98 and your biographical note On page 98 – see comment.

PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY IN PRETERM BIRTH

Prof Gamsu's contribution is on pages 54-6, 63, 84-85, 100 + biog note 114

The transcript of a Witness Seminar held by the Wellcome Trust Centre for the History of Medicine at UCL, London, on 15 June 2004

Edited by L A Reynolds and E M Tansey

11/8/05

-3 10.3.05; -4 7.07.05; -5 28.7.05;-6 4.8.05 (2nd); printed: 5 August 2005

o:\data\witness\25-corticosteroids\cortico6-040805.doc

See my comment on page 114.

Spare pages removed 21a/05

7/9/05
read + ack 9/9/05
please return by 7 Sept 2005.

Prenatal Corticosteroids for Reducing Morbidity and Mortality In Preterm Birth

Participants

Dr Mary Ellen (Mel) Avery
Sir Christopher Booth
Dr Peter Brocklehurst
Sir Iain Chalmers
Dr Patricia Crowley
Professor John Gabbay
Professor Harold Gamsu†
Dr Dino Giussani
Mrs Gill Gyte
Dr Stephen Hanney
Professor Jane Harding
Dr John Hayward
Dr Edmund Hey (Chair)
Dr Ian Jones
Professor Richard Lilford
Professor Miranda Mugford
Mrs Brenda Mullinger
Professor Ann Oakley
Dr Sam Richmond
Dr Roger Vernier Jones
Professor Dafydd Walters
Mr John Williams

Among those attending the meeting:

Professor Richard Beard, Dr Sheila Duncan, Professor Abby Fowden, Dr Anita Magowska, Dr John Muir Gray, Professor Alison Macfarlane, Dr David Paintin, Professor Maureen Young

Apologies include:

Professor Sir Robert Boyd, Dr Clive Dash, Professor Geoffrey Chamberlain, Dr Pamela Davies, Professor Sir Liam Donaldson, Professor Peter Dunn, Dr Jonathan Grant, Professor Aidan Halligan, Professor Mark Hanson, Professor Ross Howie, Professor Frank Hytten, Professor Marc Keirse, Professor Sir Graham Liggins, Dr Jerold Lucey, Professor Sally MacIntyre, Dr Jonathan Mant, Professor Jim Neilson, Dr Cliff Roberton, Ms Barbara Stocking, Dr Peter Stutchfield, Dr Peter Williams, Professor Mark Walport, Professor Jonathan Wigglesworth

†Died 31 August 2004

> In total contrast, the lungs of the other remained solid and liver-like, and sank.[18]

There are a couple of things that interest me about these descriptions. One is the unique pairing of an experimental scientist who was also an obstetrician, with the only paediatrician in the country who was capable of looking at [after] the [?premature?] babies. Another is that whatever the later perceptions became, it's clear that both the authors of the study were involved together from the beginning, in the animal laboratory, as well as in the clinical aspects.[19] Finally, I am entranced with Ross's comments that this lamb trial was simply a sideline for both of them. It's an interesting warning against the narrow and predetermined endpoints of some research programmes, and highlights the importance of serendipity in progress.

Ross describes presenting the results of the completed study – not the initial part of the study that was published in 1972, but the completed study – at a symposium hosted by the Royal College of Obstetricians and Gynaecologists of the UK in 1977.[20] He said to me, 'They didn't really want to hear'. He also

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[18] Quoted from 'Prenatal glucocorticoids in preterm birth: a pediatric view of the history of the original studies', a draft memoir by Ross N Howie dated 2 June 2004 and distributed at the Witness Seminar. It will be deposited along with other records of this meeting, GC/253, in Archives and Manuscripts, The Wellcome Library, London.

[19] Professor Ross Howie wrote: 'Jane Harding is too kind in saying that I was involved in Mont's animal work from the beginning. Our contacts were occasional. I do remember what may have been the start of his work, a visit to the Ruakura Animal Research Station, the leading institution of its kind in the country, about 120km south of Auckland, probably between 1962 and 1965. I have an idea this visit was facilitated by Sir William (Bill) Liley of fetal transfusion fame. Contacts in Ruakura would have helped Mont with his work, notably Bob Welch. But animal work was not my thing; in any case I had too much else to do.' E-mail to Mrs Lois Reynolds, 12 June 2005. For details of the Liley chart to measure amniotic fluid bilirubin levels plotted against gestational age, see Zallen *et al.* (2004): 11–12. See also Appendix xx, page xx.

[20] Dr Clive Dash wrote: 'At the time when Ross Howie presented the results to RCOG in 1977, the UK study was in its recruitment phase. Whether knowledge of the status of the UK study played any part in the cool response of the delegates at the meeting, which Ross sensed, would be speculative.' E-mail to Dr Daphne Christie, 10 January 2005.

reported that when he was asked for a recommendation as to what people should be doing, he said that the treatment looked very promising, but that it would be unsafe to initiate a new treatment on the basis of a single trial. He said that he knew what he should do, but that others should wait for ongoing trials. Other people here can talk about the progress of the treatment after that time. My own involvement began perhaps when I entered medical school in 1973. Both of the principal actors were my tutors. The use of antenatal steroids was routine at that time in our hospital and has remained so ever since. By this time Mont had moved onto other studies. Ross was completing the four- and six-year follow up of the original cohort, funded by the World Health Organization.[21] He always believed very strongly that long-term follow up was essential for anything in neonatal care and set about this with his usual thorough approach. The follow-up studies were published in the early 1980s and the ongoing follow-up studies we will talk about later.[22]

Hey: Would you like to explain why they chose the steroids they did, because a lot of people never seem to have noticed. Most people think that if they are using betamethasone they must be using the product that Ross and Mont did. They think it is betamethasone, full stop.

Harding: I can tell you that story because I specifically asked both of them in recent weeks. To paraphrase a long story: Mont had been doing work in human pregnancy on the effects of steroids on the fetus, and he had a reasonable idea of what dose of steroid was required to suppress progesterone production and he presumed that that would be an adequate dose to do

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[21] WHO studies????? MacArthur B A, Howie R N, Dezoete J A, Elkins J. (1981) Cognitive and psychosocial development of four-year-old children whose mothers were treated antenatally with betamethasone. *Pediatrics* **68**: 638–43. ? Harding J E, Howie R N. (1987) First-year mortality and hospital morbidity after newborn intensive care. *New Zealand Medical Journal* **100**: 548-52. For erratum, see *New Zealand Medical Journal* (1987): 642.?

[22] Follow-up studies here.

something to the fetus. He knew that he wanted something that would be reasonably long-lasting, so that it didn't have to be given too frequently to pregnant women and decided that something that would last for 24 hours and therefore two doses would give you about a 48-hour effect would be adequate, based on the animal studies. He therefore set about looking for a drug that would be clinically easy to manage, long-lasting, and which had an identically appearing placebo. This is not easy, because all the long-lasting preparations of glucocorticoids are opaque, they are milky substances, and a placebo wasn't easy to find. He wrote to a number of drug companies asking for help, and in the end Glaxo – originally the name of a dried milk power sold by a New Zealand company, and it so happened that the medical director was a mate of Mont's – provided an opaque placebo.[23] Their long-acting preparation was the one he used, because that was the one that was available and they were provided with the placebo. So the placebo was cortisone acetate, which had very low potency but looked the same, and the drug that he selected was the Glaxo drug because that was what was available and because the director was a mate who provided it for free. I might say that the study was unfunded. Mont said to me, 'We didn't need funding to do this trial.' And of course they didn't, because the drug was provided free and both Mont and Ross were fully salaried and were able to put in all of their time.

Hey: Just remind us how many babies were eventually recruited.

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[23] Dr Clive Dash wrote: 'Because of the Glaxo link, it was well-known in the UK which product had been used in New Zealand [Gamsu *et al.* (1989)]. The NZ product was an ester of betamethasone (acetate), the properties of which caused a slower absorption from the intramusclular site than the very soluble product (phosphate salt) available in the UK. It was estimated that more frequent injections of the soluble product would give a similar bio-availability. The placebo used in the UK was specially prepared for the study by Glaxo and consisted of the vehicle in which the phosphate salt was formulated. Both were clear solutions in identical vials and labelled similarly except for patient numbers assigned randomly. Thus, the blind was preserved.' E-mail to Dr Daphne Christie, 10 January 2005.

Harding: Twelve hundred. The real number was 1218.

Hey: Still the biggest trial.

Harding: Still the biggest trial. The original publication that everybody cites from 1972 was only the first 282. But they continued to recruit long after that trial.

If I could just comment. The other thing that most people aren't aware of is that after the first 717 women were enrolled, when they did the first analysis and thought 'the stuff really does work', they doubled the dose. In the rest of the trial, the other 500 odd actually received twice the dose, to see whether more was better, and they concluded that it was not, and published all of the data as a combined single trial.[24]

Hey: May I just ask one other question? I get the impression that the gap between their having the recognition that it worked and starting the trial was pretty short. The trial started in December 1969, and it's there in print in July 1972.

Harding: That's correct.

Hey: Were the first patients actually randomized? Did they start right from the beginning?

Harding: They truly did start randomizing at the end of 1969 and it really was the beginning of the trial. In his usual way Mont decided that the animal studies were conclusive and that they should move on to [human] trials. When

[24] 1976 results?

this because I know a little bit about the history[28] of the National Women's Hospital in Auckland and it doesn't have a very good history itself in terms of ethics of trials. So I just wondered what the original protocol for this trial said about seeking consent and giving information to the parents of these babies.

Harding: I have to tell you I have never seen a detailed trial protocol. I have seen the paper that went to the senior medical staff committee and it does say that women would be asked to consent to randomization. It would have been verbal consent.[29] And like you and a number of other people, I wondered how real and how effective that process was at the time. We will talk further later I am sure, but we have just completed the 30-year follow up of these babies, and one of the things that we had some concerns about is about how people would react to being approached 30 years later about a trial where we weren't sure how informed the consent was.[30] We have been overwhelmingly impressed with how positive people were about the trial. In the end we traced 72 per cent of the original participants and a number of the children, now 30-year-olds, who obviously did not know they were part of this trial, and who went back to

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[28] Prof Oakley, could you elaborate further about this? It would make a good footnote.

[29] See Appendix xxx, page xx.

[30] Dalziel S R, Walker N K, Parag V, Mantell C, Rea H H, Rodgers A, Harding J E. (2005) Cardiovascular risk factors after antenatal exposure to betamethasone: 30-year follow-up of a randomized controlled trial. *Lancet* **365**: 1856–62. Niven G R, Harding J E. (1995) Another outcome of neonatal intensive care: first year mortality and hospital morbidity. *Journal of Paediatrics and Child Health* **31**: 137–42. Harding J E, Howie R N. (1987) First year mortality and hospital morbidity after newborn intensive care. *New Zealand Medical Journal* **100**: 548–52.

Mrs Brenda Mullinger, who had worked with Prof Gamsu, wrote: 'Prof Gamsu was also disappointed that we did not learn more from Prof Jane Harding of the follow-up data from the original Liggins and Howie in New Zealand, even though this was promised in the earlier part of the Witness Seminar. Will it be possible to include a brief synopsis of their findings? The idea of undertaking a follow-up of babies born in the UK study was mentioned at the seminar – this is a real possibility because Prof Gamsu was diligent in retaining all the trail record forms (and randomization codes) long after others' interest in the study had ceased.' Letter to Dr Daphne Christie, 6 January 2005.

their mothers and sometimes we traced the mothers rather than the children. There were a few women who did not recall being part of the trial. I think that's not surprising given the circumstances. Remember that the tocolytic used during the first three years of the trial was ethanol. IV ethanol was the tocolytic used until about 1971.[31] However, the vast majority of women did recall that they were in the trial and recalled it very positively. A number of the subjects, the offspring, the children – now adults, I don't know how to call them because of that difficulty – came along because they said their mothers told them they had to come. Their mothers were so grateful that they had been part of the trial, that their preterm baby had survived as a result of this trial, as they perceived it, and were very positive about it. That's a slightly long answer to your question. I think consent really did happen, it was verbal consent, and the reaction of the majority of people involved was very positive 30 years later.

Mrs Gill Gyte: I am interested also in the women who were in the control arm. Did you get a similar sort of response, 30 years later?

Harding: The vast majority of participants still do not know which group they were in. So in terms of the 30-year follow up, most of the people that came along were convinced they had had steroids because their babies survived, and we have done our best not to unblind them, because we think a further follow-up is going to be fairly critical for reasons that we might talk about later. So women simply know they were in a trial and have a surviving baby, because obviously we didn't trace the mothers of the babies who did not survive.

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[31] Dr Clive Dash wrote: 'The UK study was being planned at the time of the move from ethanol as a tocolytic to various newly introduced β-agonists. We decided to use salbutamol, if a tocolytic was clinically necessary, so as to standardize one of the management modalities – and also because salbutamol had been developed by Glaxo.' E-mail to Dr Daphne Christie, 10 January 2005.

Universite de Paris], the fellow who is still publishing on 'beware, beware,' and I cannot counter that.[53] I'm glad he's looking at it, and I just think we have to be vigilant and [?that?] those of us who spend more time with this have to keep track of the babies.

Lilford: Since this is a history meeting, and while you have been talking about the early 1970s, I have been thinking back into the recesses of my own mind. I was a young doctor in Cape Town and news about this crossed the Indian Ocean and people were interested there. As I can recall it, there seemed to be a notion that many babies would, in retrospect, be found not to have needed antenatal steroids because their lungs were very mature. And so the idea that was being put around then was that one should test first to see if the lungs were already mature. And the person who did that testing was me. So if somebody needed early delivery, then I would do an amniocentesis. We had a thing called a bubble test and I would take the fluid off to a side room and I would mix it with alcohol.[54] I would shake it and then there was this chart on the wall where the bubble density could be related to maturity. If there were more than a certain number of bubbles, then we could safely proceed with the delivery the next day. If there weren't, then we gave steroids. We would re-test two days later and if there were now bubbles we knew we could go ahead with delivery. So there must have been another scientific climate running at that time which said that [?we should?] discriminate more before we shove these steroids in. But as far as I know, that line of thought ran into the sands, it didn't progress in any way. I just mention that for your edification.

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[53] [Prof Avery, is this the correct Burri ref? If not could you suggest one?] Corroyer S, Schittny J C, Djonov V, Burri P H, Clement A. (2002) Impairment of rat postnatal lung alveolar development by glucocorticoids: involvement of the p21CIP1 and p27KIP1 cyclin-dependent kinase inhibitors. *Pediatric Research* **51**: 169–76. See also Avery M E. (1975) Pharmacological approaches to the acceleration of fetal lung maturation. *British Medical Bulletin* **31**: 13–17.

[54] Prof Lilford, could you expand on the bubble test? Our readers would find this technique of interest.

Mrs Brenda Mullinger: At the time of the UK multicentre trial, I was working for Glaxo and I coordinated the trial in the UK.[55] What I wanted to say relates to what Professor Crowley said about uptake. Although we originally coordinated the study after different clinicians had approached Glaxo, we found that we needed more centres to join the study, and so we did actually try approaching [?approach?] other centres in the UK. Looking at the paper [now?] we got underway in mid-1975, but I was told by Dr Clive Dash, the medic at Glaxo who unfortunately cannot be here, that many of the UK centres who were approached wouldn't join the study because they were already using betamethasone and they felt that it wasn't ethical to have control groups. So that although your uptake maybe was only 10 per cent, certainly the research centres, the sort of centres that might have joined the study, were starting to think about using it by the mid-1970s in the UK.[56]

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[55] Mrs Brenda Mullinger wrote: 'The UK multicentre trial was conducted from mid-1975 to February 1978; 251 women were randomized to double-blind treatment with either betamethasone phosphate (4mg every eight hours for a maximum of six doses) or matching placebo, each given by intramuscular injection. Betamethasone treatment reduced the incidence of RDS relative to placebo – the greatest benefit was seen in those infants born before 34 weeks' gestation. See Gamsu *et al.* (1989).' Note on draft transcript, 6 January 2005.

[56] Dr Clive Dash wrote: 'The UK multicentre study [Gamsu *et al.* (1989)] was designed in 1974, largely stimulated by the publication of Liggins and Howie (1972) and their prior animal studies. The idea for a UK study was an amalgam of interest from some obstetricians and neonatal paediatricians and from within the Medical Department of Glaxo in the UK because of the organizational link with the Antipodes. A taxing question in the design and analysis of the UK study was the imprecision in estimating gestational age at the time of recruitment. Maternal dates and obstetrical palpation were the only antenatal assessments available then – so different from the current techniques! The clinicians documented both estimates for the analysis. These were augmented (or confounded) by neonatal assessment [Farr *et al.* (1966); Dubowitz *et al.* (1970)], which was also recorded. Clinicians' views can change during the planning and conduct of long-term studies (about 4 years to plan and complete recruitment and follow-up for the UK study). All the clinicians involved in the early planning recognized that more clinical work was needed to confirm the results from New Zealand. Everyone involved in the study's planning recognized that it was important to have commitment from an obstetrician and paediatrician at each participating hospital. By the time the study recruitment started (about one year later), some of the clinicians did not wish to recruit patients to the study for various reasons, even after Ethics Committee approval.' E-mail to Dr Daphne Christie, 10 January 2005.

trial completed and published more than five years ago, that they can still find the original raw paperwork? One of the most amazing things that I found in reading around before today's meeting, was to come across this paper by a Jane Harding in the *American Journal of Obstetrics and Gynecology* on just this subject, published in 2001, and this is control trial data, and it has sat there all that time.[82]

Harding: Yes. I think there are a number of messages. One is the data was still there and still in a form that we could use, which I think is very impressive. The second is that new questions have come up that the trials weren't necessarily designed to answer at the time, but it's terribly important that the data is still there.[83] Thirdly, someone might like to comment on the length of time it took us to get that paper published. The study was done in 1996–97, we wrote it up in 1998, it was rejected by two journals, submitted to the *American Journal of Obstetrics and Gynecology* in 1999, and it was eventually published in 2001. I do think the people who publish have something to contribute to this very prolonged process.

If I could just go onto the other issue that was raised, what about the women who get steroids and don't deliver? We have been concerned about this with respect to the repeat steroid issue. There has been a multi-centre randomized trial being run by Caroline Crowther out of Adelaide for the last seven years.[84] We hope to finish recruiting this month. It includes 980 women, and we have been doing huge detailed studies of the babies in Auckland, the second largest centre recruiting to this trial. It occurred to us early on in that trial that we still

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[82] Harding *et al.* (2001).

[83] See Peter Elwood's description of planning the Caerphilly study in Reynolds and Tansey (eds) (2005): 81.

[84] See also Crowther C A, Harding J. (2003) Repeat doses of prenatal corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2003. Chichester: John Wiley & Sons, Ltd.

didn't have good data about risks and benefits for that group [?:which??], the group who don't stand to achieve the greatest benefit for the infant and are potentially at the greatest risk. Once again we thought the data wasn't out there but I bet it was in the original trial. Once again we were able to go back to the original data, look specifically at that group, write a new meta-analysis which has also been published after many rejections, after a very long time, which showed, in fact, that there may be adverse effects in that group.[85] Therefore people need to randomize them to the new trials. We were in fact trying to help recruitment of the randomized trials. It took so long to publish that. I think it's had very little effect on recruitment to the trial, but the data are nevertheless there. Yet another outcome that was not relevant at the time, the question has come up subsequently.

Hey: Would Glaxo still be able to find the data?

Professor Harold Gamsu: Oh yes, I have all the data in my office.[86] It's still there, all the data sheets, because I was hoping to do a long-term follow up on

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[85] McLaughlin *et al.* (2003).

[86] Gamsu *et al.* (1989). See? Protocol and case record, in Figure ??? Dr Clive Dash wrote: 'The retention of clinical trial data in the 1970s–80s was poor. This has changed in recent years. When Harold Gamsu persuaded us to do a detailed analysis of the UK study, the computer software had changed and so had most personnel acquainted with the prior system. Luckily, Alex Paton at Glaxo was able to interrogate the database and through her efforts we were able to meet Harold's expectations and answer his critical questions. Also, Harold volunteered to keep safe the original case record forms and other study documentation when Brenda Mullinger and I left Glaxo to pursue other career opportunities. I believe Harold always hoped to trace the babies in adult life to address the question of the long-term safety. It is due to his diligence and enthusiasm that he persuaded us (again, pleasantly) in 2001 to begin the process towards a 30+ years follow-up. His untimely death occurred in August 2004, soon after this Witness Meeting. We hope to continue this project with the support of NPEU in Oxford provided external support can be mobilized and plan to dedicate any outcomes to his memory.' E-mail to Dr Daphne Christie, 10 January 2005.

Q to Dr Tilli Tansey:
Would you like a copy of the protocol and case record form? They are too lengthy to go as footnotes. It would need an Appendix to the publication. Please contact Brenda Mullinger or myself if needed. CJ ask

Recd 21/10/05

the adults, and in fact things haven't turned out that way, but that's still available for people to do if they would like to.

Hey: Because people are still asking the questions: 'Does it work in twins?' or 'Should you give it in mothers with hypertension?'

Gamsu: Our numbers, of course, are very small.

Hey: So are everybody's, but if people have kept their data, there are more that can be analysed that has not yet been done. Could anybody find the NIH data? Would the NIH people share their data?

Avery: I have no idea.

Gamsu: May I ask a question about this study by Newnham and Co? My feeling is that it is animals, but could you tell us a little bit more, because it sounds very significant if it's not animals.

Brocklehurst: I cannot tell you very much more, because I heard it presented in Glasgow about six weeks ago, but I have seen nothing in the press yet.[87] My recollection is that it was in animals, but we'll be able to explore this further

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[87] Professor John Newnham from the King Edward Memorial Hospital, University of Western Australia, Perth, Australia, delivered the Society Lecture, 'Antenatal Steroids and Outcome', at the British Maternal and Fetal Medicine Society's Ninth Annual Conference, 1–2 April 2004, held at the Scottish Exhibition and Conference Centre (SECC), Glasgow. He presented results from human and animal studies where infants had been exposed to steroids before birth. See the full report by Dr Margaret M Ramsay, Honorary Secretary, BMFMS at www.bmfms.org.uk/presssummaryofglagow04.doc (visited 18 July 2005).

when the study is published.[88] Having tried to do one of the large trials of multiple courses of steroids, I think one of the issues with clinicians about the use of multiple courses of steroids is that their threshold for starting antenatal steroids is lower, because if they are wrong, and the woman doesn't deliver soon, they have felt that they can always give a second course. If people are restricted to giving a single course of steroids they may delay starting until there is stronger evidence, if you like, of impending preterm birth. So the groups of women selected into these trials is likely to be quite different from the multiple steroids group and that will make the interpretation of the results interesting.

Lilford: I recently had a debate with my 14-year-old daughter Philippa about whether history is just an interesting thing to read, or whether it helps us to design our own futures. Listening to Jane speak makes me think that there really are occasions when history has a lesson for the future. Hearing you speak about finding these records has been very interesting, but I suspect that many people in this room were amazed that you really could find those source materials after 30 years, that you could find the trial documents and so on. When Harold Gamsu moves the documents from his office, goodness knows where they might go. So the lesson that we might want to learn from this is the importance of some sort of systematic paid for-archive for trial information and I don't know if you might want to comment. I know that the Economic and Social Research Council (ESRC) archive their most precious data and build the cost of so doing into the grant.[89] The more I hear the more I think this might be something we ought to try to take forward as a matter of some urgency.

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[88] The lecture will be published in 2006 as: Newnham J P. (in press) The steroid story: iconic advance or ticking bomb? *Yearbook of Obstetrics and Gynaecology*, vol. 12. London: The College.

[89] The Economic and Social Data Service (ESDS) Qualidata is a specialist service of the ESDS led by the UK Data Archive (UKDA) at the University of Essex. The service provides access and support for a range of social science qualitative datasets. Established in 1967 the UKDA holds the largest collection of digital data in the social sciences and humanities in the UK, funded by the ESRC,

Apart from power, I think that vested interests, empire building and struggles and political competition between trusts were barriers – this was the time of the purchaser–provider split and market competition was a really important issue around 1995/6. The main barrier was fear of something going horrendously wrong. People would then distort their perception of the evidence and vigorously resist on being told to do something that they didn't think was safe to do, regardless of the evidence. After about six months the staff went through a series of educational events at this particular hospital and eventually decided to start to introduce ECV and as far as I know it is now common policy. But we couldn't make them do it, they had to decide to do it themselves, and they had to take their clinicians with them. I think it was a painful and difficult process for them everyone.

May I just mention the main conclusions from this particular piece of work? Don't expect this sort of study to get it into the *British Medical Journal*. It won't be accepted. Secondly, advocates are really important when it comes to getting guidelines adopted and I think opinion leaders are really important within institutions, but the important thing is that the guidelines have got to be written in such a way to be usable, understandable and accessible to those who are going to implement them. That means clear inclusion and exclusion criteria. Another important agent for change are the users, and if you have women asking these sorts of questions, after a while people do get a bit embarrassed coming up with the same answers that clearly won't be supported by evidence or by colleagues. I would like to see women users being far more involved in ways in which we can encourage the implementation of best practice. I am not surprised that there was no sign of managers actually implementing any change in Richard's study. It's a scary business. There was blood all over the carpet when we were dealing with the ECV meetings, and it required somebody – like the users who were tough, or somebody like me who's a public health specialist and who has been a GP and is not afraid of consultants – to hold the line if necessary. Managers cannot do that, and I don't think we should expect them to. I think it's exceedingly difficult. The

most important barrier, the most important influence to achieve change, is the personal experience of the person making the clinical decision. When new interventions are being rolled out we must encourage people to be at the centre of it, so they get feedback of the positive results. Then it is much easier to get change implemented.

Hey: That rings true for a lot of us, I think. You went over time, but I think you said something very important. We are beginning to get very tight for time and so I am going to ask Stephen Hanney to speak next. But Harold [Gamsu], while you were out of the room we did hear that quite a lot of units said that they couldn't join your trial, because they were already using it so widely and that occurred at the time when in actual fact we know that ess than 6 per cent were really using steroids nationally l. Did being involved in the trials themselves influence the centres? Did the centres that had been involved in the research take up the outcome of that research more than those who only read about it?

Gamsu: I don't know the answer to that I am afraid. We didn't follow that point up, but as far as I know Brenda Mullinger might know something about it. All I can say is that there were local reasons that indicated against the use of steroids. There was quite a lot of gossip about this and we have heard some examples of this today. The risk of infection especially in ruptured membranes, and the unexplained deaths in hypertensive women from Liggins's original report which turned out to be spurious.

The other thing that I found was influencing obstetricians was the increased risk of pulmonary oedema which people widely accepted as a complication of steroid therapy. In fact it was a complication of tocolytic agents that were used, especially when those agents were given in large volumes of fluid. As far as I know, steroids given alone were not tocolytic agents and did not result in pulmonary oedema. So I think we had quite a lot of persuading to do even in

those places that accepted that they would be in the trial. I know that Brenda Mullinger and Clive Dash from Glaxo had a lot of difficulty keeping the momentum up, trying to recruit women, even though ..... ~~[?] were reaching~~ the ~~volunteers.~~ As you possibly remember from the paper, 60 per cent of the cases came from patients who were recruited from three hospitals, the rest of them just put it away.

~~Hanney~~: We at Brunel have been looking at the benefits from health research for about ten years now, and this particular stream of work seems to us to have been one of the most interesting, and [that] I have worked on ~~it~~ with Miranda, Martin Buxton and Jonathan Grant. I apologize for checking my notes from time to time, because I am trying to pick up what various people have said today in what I think is an interesting session.

For instance, John [Hayward], we at least read your work. There is a paper that sets out most of this in detail in press and will be published in *Social Science and Medicine*.[147] I will just highlight all the key points for now. Perhaps it's just worth spending a minute, going over our payback framework so you can see how we tried to drop this stream of work into a frame [?model?] that we had already developed. Apologies to those who have already heard this many times before. Basically, there are two aspects to our payback framework: a multidimensional categorization of benefits, and a model to examine how they arrive. The categories which we suggest are five: knowledge production; the targeting of future research and building research capacity; better informing policies, with the term policies being widely interpreted; health gain and benefits to the health sector; and the broad economic benefits. There's a series of stages in the model in which we think these various benefits can be identified. A key feature of our model is to attempt to identify actual levels of uptake so that we can then say what the benefit has been, and this, of course, links with previous discussions.

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[147] Hanney *et al.* (2005).

There's always a problem when doing this type of analysis as to where you start. Various initial presentations today showed clearly that research builds on previous research etc., and so whenever one makes [?chooses?] a start[ing] point, it is always artificial. On the other hand I do think the nature of the discussions [?today?], and what Mary Ellen says, does provide [?has provided?] a realistic basis for saying we will start by looking at the work of Liggins and Howie. In terms of knowledge production clearly the 1969 paper from Liggins, [and] the 1972 paper from Liggins and Howie, were very important.[148] There are lots of weaknesses in citation analysis, but it does indicate whether people have taken notice, and these are two very highly cited papers, especially the 1972 paper which has been cited over 1200 times.[149]

There has been some bibliometric analysis in this field undertaken by the Policy Unit here at the Wellcome Trust.[150] Various generations of papers were traced backwards and showed again that this was the most important work in this field in several generations. Clearly knowledge production [is] very high. In terms of affecting future research, again citations indicate that it has influenced much subsequent work. It's also interesting that many of the other pieces of work, trials etc., actually start with a reference to the work of Liggins and Howie, which again I think emphasizes their importance for further work. And it's also been mentioned that Ross Howie felt that further trials should be undertaken rather than necessarily saying that people should act on the findings. Nevertheless, there was quite an uptake in some places, on the basis of this very important trial and the ensuing publications from it. In the UK the

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[148] Liggins (1969); Liggins and Howie (1972).

[149] Dr Stephen Hanney wrote: 'The article pre-dated the start of the electronic record of citations, therefore I calculated this figure from the post-1981 electronic data plus hard copies of ISI data from earlier years [Hanney *et al.* (2005)]. Mont Liggins had an article in the *Citation Classics* series in March 1982 and by then the number of citations for the 1972 paper was already 565.' Note on draft transcript, 12 July 2005. See Mont Liggins' article of 29 March 1982 freely available at www.garfield.library.upenn.edu/classics1982/A1982NF37800001.pdf (visited 14 June 2005).

[150] Grant *et al.* (2003).

Brocklehurst: I am conscious that I have been asked to speak about current research and where the research gaps are in a session about twentieth century medicine. So we are already a bit beyond the twentieth century in terms of what I intend to discuss, although hopefully in a few years time this will be history and you can tell me that I was completely wrong in guessing where we were going to go. I want to talk about some of the issues that have come up today in terms of how we are now looking at the evidence that we have and what is beginning to come out. I am going to discuss the issue of the use of multiple courses of steroids, but there are a couple of other issues which I wanted to touch on that have been brought up this afternoon, one of which is the choice of agent that we use for antenatal corticosteroids.

A very interesting paper has been published in the *American Journal of Obstetrics and Gynecology* by Alan Jobe and Roger Soll,[162] which looked at the available trials and separated them into those have used dexamethasone and those that have used betamethasone. The interesting thing is there have been no head-to-head comparisons of dexamethasone versus betamethasone, which have looked at substantive neonatal outcomes.[163] There have been trials that look at antenatal fetal heart rate tracings, which seems to be irrelevant if they are not related to the outcome for the baby.[164] Jobe and Soll suggest that

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[162] Jobe and Soll (2004).

[163] Dr Clive Dash wrote: 'Various preparations of betamethasone are available in different countries. The preparations are all designed to release the active sterol, betamethasone, but at different rates. The soluble phosphate preparation is suitable for intravenous administration, like hydrocortisone, as well as intramuscular injection. The acetate preparation is not suitable for intravenous (IV) use. Some products are a mixture of the acetate and phosphate derivatives (e.g. *Celestone*®, Schering). In some countries dexamethasone is more readily available than betamethasone and this is why it has featured in some studies. These two steroids are isomers in which the methyl group differs in its orientation (dexamethasone is 9-α-fluoro 16-α methyl prednisolone; betamethasone is 9-α-fluoro 16-β methyl prednisolone)[Sweetman (2002): 1063 and 1067]. In the usual pharmacological tests of corticosteroid potency, they are equivalent. In general, the mode of action (pharmacodynamics) seem similar, so they should be therapeutically equivalent.' E-mail to Dr Daphne Christie, 10 January 2005.

[164] See for example, Senat MV, Minoui S, Multon O, Fernandez H, Frydman R, Ville Y. (1998) Effect of dexamethasone and betamethasone on fetal heart rate variability in preterm

betamethasone is preferable to dexamethasone, because the betamethasone trials, compared with placebo, have a marked reduction in the incidence of death, and [while?] dexamethasone has no statistically significant effects on neonatal death. Although one of the things they reported is the fact that the number of trials using betamethasone is substantially larger than the number of trials using dexamethasone, and the numbers of participants in each trial of betamethasone are larger.[165] However, they have suggested some biological plausibility for this, and I am sure we are going to see a lot more about what agent we should be using. One of the issues that they raised is the availability of the drug, because no drug companies hold a licence for steroids for antenatal indications, the ability to get hold of dexamethasone and betamethasone in the US is becoming more and more difficult, because no company is producing it, because it doesn't have a licence. So people are using all sorts of other steroids, some of which clearly do not cross the placental barrier and may not be effective at all. They also raise issues about whether oral steroids may be as good as intramuscular steroids and also discuss different ways of giving steroids to the baby, whether you can give it into the intra-amniotic fluid, or give it directly intramuscularly into the fetal thigh, which seems a little bit more invasive than a quick intramuscular injection into the mother's thigh. I suspect we are going to see a lot more about the choice of the agent in the future.

We have heard a lot about long-term follow up after a single dose of antenatal steroids and the 30-year follow up of the original Liggins and Howie trial will be extremely useful. I think we probably need to do more follow up, much longer-term follow up of the other trials that have been done to try to strengthen the evidence base on the long-term effects, if only to be reassured

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labour: a randomized study. *British Journal of Obstetrics and Gynaecology* **105:** 749–55. Subtil D, Tiberghien P, Devos P, Therby D, Leclerc G, Vaast P, Puech F. (2003) Immediate and delayed effects of antenatal corticosteroids on fetal heart rate: a randomized trial that compares betamethasone acetate and phosphate, betamethasone phosphate, and dexamethasone. *American Journal of Obstetrics and Gynecology* **188**: 524–31.

[165] See note 75, Liggins to Howie, 11 Jan 2005.

multiple courses of steroids. So it looks likely that we may end up with about 3000 women recruited around the world in trials on multiple courses of steroids versus the a single course, instead of the 10 000 women. I am very sceptical whether in five years time we will actually have enough information to answer the question of the long-term outcomes. The short-term respiratory outcomes look as if they may be favourable for multiple courses of steroids, but clearly that is only part of the question. So the fact that we didn't get the original trials into practice very quickly has not necessarily taught us to improve on past performance when it comes to antenatal corticosteroids.

The other thing to mention, I suppose, is that in the absence of trial evidence about long-term outcome, people will rely on observational studies of long-term outcome. The one observational study with repeated courses of steroids which has been published is from the Western Australian group, which suggested a statistically significantly decreased incidence of cerebral palsy with multiple courses of steroids versus a single course, but a statistically significant increase in significant behavioural problems among the children who survived to the age of six years.[171] I was discussing this with Jane [Harding] during the break this afternoon that in Australia and New Zealand the amount of steroid used is going down. I think it is going down in the UK when I talk to clinicians, because of these uncertainties and concerns about the harm associated with multiple courses of steroids. How we ever get people to interpret what we say correctly, I am not sure. Clearly the messages that are coming out at the moment are not that steroids are bad, but that we need to be more sophisticated in how we use them and how that information is interpreted appears to be to stop using them.

The issues for the future in terms of our current gaps are: the biggest one is that we cannot currently identify women who are going to deliver preterm very effectively. We can agree we are going to deliver them preterm electively, but

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[171] Is this the correct Western Australia group reference?? Ee L, Hagan R, Evans S, French N. (1998) Antenatal steroids, condition at birth and respiratory morbidity and mortality in very preterm infants. *Journal of Paediatrics and Child Health* 34: 377–83.

for the vast majority of women who deliver spontaneously, we are not very good at recognizing them. And things like fetal fibronectin and cervical length on ultrasound screening may help us to identify a group of women who are at a much higher risk of preterm delivery, and we can target our intervention more effectively. I am sure that we will see much more of this in the future.

As to the gestational age at which to use steroids, what formulation, what dose, and what route of administration, I think these are questions that we will have to tackle in the future. What gestational age to give steroids? Nobody has mentioned yet the trial that has only been published in abstract that Peter Stutchfield did in Wales where they recruited women who were going for elective caesarean section at greater than 37 weeks.[172] They randomized nearly 1000 women to receive steroids or not and showed a significantly decrease in admissions to the neonatal unit with respiratory symptoms in the group given [receiving?] steroids. So even beyond 37 weeks, if you deliver electively by caesarean section, steroids seem to offer some advantages. The issue about whether there is a cut-off when you don't give them is going to be re-opened. The multiple course of steroids debate is, as I said, still wide open, although we will see more evidence about this over the coming years, and it may hopefully answer some of our questions.

A big lesson that has come out of the steroids trials – not only antenatal steroids, but postnatal steroids – is that with perinatal interventions we really, really have to look at the children, if not the mothers as well, in the longer term, because these babies don't stop developing the minute they are born, they go on and on and on.[173] I was reading in *Time Magazine* recently about a study where they had done serial MRI scans in teenagers and they are suggesting that the brain does not stop developing until age 25, which seems a

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[172] Where was the abstract printed?

[173] Dr Clive Dash wrote: 'The response by the delegates at the RCOG meeting in 1977 may also have been tempered by the anxiety, certainly among many clinicians with whom I spoke at that time, that the long-term effects might prove to be significant.' E-mail to Dr Daphne Christie, 10 January 2005. See also note 20.

Sir Iain Chalmers

FRCPE FFPH FMedSci (b. 1943) has been Editor of the award-winning James Lind Library since 2003. He was Director of the UK Cochrane Centre in Oxford from 1992 to 2002 and Director of the National Perinatal Epidemiology Unit, Oxford, from 1978 to 1992. See www.jameslindlibrary.org/ (visited 2 June 2005).

Professor Archie Cochrane

CBE MBE FRCP FFCM (1909–88), medical scientist and epidemiologist, whose first clinical trial was conducted as a prisoner of war in Salonika. Following the war he was appointed to the Medical Research Council's Pneumoconiosis Research Unit in 1948. In 1960 he was appointed David Davies Professor of Tuberculosis and Diseases of the Chest at the Welsh National School of Medicine, Cardiff, becoming Director of the Epidemiology Research Unit there in 1961 until his retirement in 1974. His papers are available for study at the Cochrane Archive, Llandough Hospital, Penarth, Cardiff. See Cochrane (1976); Cochrane [ALC] (1988). See also Ness *et al.* (2002).

Dr Patricia Crowley

FRCOG FRCPI (b 1951) has been a consultant Obstetrician Gynaecologist at the Coombe Women's Hospital, Dublin, and Senior Lecturer at the Department of Obstetrics and Gynaecology, Trinity College Dublin since 19xx.

Dr Clive Dash

FFPM (b. 1940) graduated from University of Birmingham and did post-graduate obstetrics with Professor Hugh McLaren in Birmingham, and has spent most of his professional life in clinical research within the pharmaceutical industry. He instigated and coordinated the UK trial of antenatal steroids in 1974 while working as a clinical research physician for Glaxo in the UK. He has been an independent consultant in healthcare and pharmaceutical medicine since xxxx, while continuing his clinical practice in thoracic medicine.

Professor Geoffrey Dawes

CBE FRCOG FRCP HonFACOG FRS (1918–96), qualified at Oxford in 1943, spent a year? at Harvard in 1946. He was Director of the Nuffield Institute for Medical Research, Oxford, from 1948 to 1985., as well as a Governor of Repton, 1959–88, and Vice President of the Royal Society, 1976–77. See Liggins G (1998). Geoffrey Sharman Dawes, *Biographical Memoirs of Fellows of the Royal Society* 44: 110–25.

Professor John Gabbay

FFPHM (b. 1949) qualified in medicine at Manchester in 1974. After working on the social origins of medical knowledge for seven years at the University of Cambridge, he trained in public health and carried out qualitative research on NHS management and clinical audit in the 1980s. From 1992 until his retirement in 2004 he was Professor of Public Health and Director of the Wessex Institute of Health Research and Developmentat the University of Southampton, which houses the National Coordinating Centre for Health Technology Assessment, of which

he was former director. His recent research has focused on the implementation of evidence in clinical practice.

Professor Harold Gamsu

FRCP FRCPCH (1931–2004) graduated in Johannesburg in 1954. His training in paediatrics commenced there, and continued at the University of Sheffield and xx in Cleveland, Ohio. He was appointed as Wates Fellow at King's College Hospital, London, in 1965, then Senior Lecturer, Reader in Paediatrics and Director of the Neonatal Unit, 1979, and in 1994 Professor of Neonatology until his retirement in xxxx, later Emeritus. He established the London Perinatal Group in the 1970s, later known as the Thames Regional Perinatal Group.

Dr Dino Giussani

PhD (b. 1967) received his PhD in Fetal Medicine at UCL and has conducted post-doctoral work at the University of Chile and Cornell University. He was appointed university lecturer at the University of Cambridge in 1993; has been Fellow of the Lister Institute for Preventive Medicine there, since 2001 and a Reader in Developmental Cardiovascular Physiology and Medicine since 200x, and Director for Studies in Pre-clinical Medicine at Gonville and Caius College, Cambridge, since 200x.

Mrs Gill Gyte

MPhil (b. 1948) has been an antenatal teacher with the National Childbirth Trust (NCT) since 1985. She was a volunteer worker on the NCT Research and Information Group from 1990 to 1997 and has been the Consumer Panel Coordinator for the Cochrane Pregnancy and Childbirth Group since 1997.

Dr Stephen Hanney

PhD (b. 1951), trained as a political scientist, has specialized in examining evaluation and policy making in higher education and research. Since 1993 he has worked with [Professor] Martin Buxton at the Health Economics Research Group, Brunel University, London, developing and applying techniques of assessing payback or benefit from health research.

Professor Jane Harding

ONZM DPhil FRACP FRSNZ (b. 1955) obtained her medical degree at the University of Auckland in 1978 and completed a DPhil in fetal physiology at the University of Oxford in 1982. After specialist paediatric training in New Zealand and a postdoctoral fellowship at the University of California at San Francisco, she joined the faculty of xx at the University of Auckland in 1989 and was appointed Professor of Neonatology in 1997. She works as a specialist neonatologist at National Women's Hospital. She also heads the fetal physiology laboratory and is Deputy Director of the Liggins Institute at the University of Auckland.

Dr John Hayward

FFPH(b. 1946) was in general practice for 16 years before re-training in public health. From 1994/6 he led the Effective Care Project in maternity services for the Camden and Islington Health Authority.

He died on 31 August 2004 (BMJ 2004; 329:1347) ✓

This reference is to his Obituary

BPL

20 September 2005

Dear Lois

Here are the documents. I am sorry the protocol is not a good, clear document, but I hope you can use it. If not, we could retype it!

With compliments from Clive

Bio Products Laboratory
Dagger Lane
Elstree
Herts. WD6 3BX
Telephone: 020 8258 2200
Fax: 020 8258 2601

A unit of the National Blood Authority.
A Special Health Authority within the NHS.

Returned 22/9/05.

PROTOCOL FOR THE USE OF CORTICOSTEROIDS IN THE PREVENTION OF RESPIRATORY DISTRESS SYNDROME IN PREMATURE INFANTS

PURPOSE OF THE STUDY

To investigate the effectiveness of betamethasone 21 phosphate ('Betnesol' - Glaxo Laboratories Ltd) in preventing respiratory distress syndrome in the premature foetus (< 34 weeks gestation).

RATIONALE

There is evidence from animal studies that surfactant is secreted into the foetal lungs if stimulated by corticosteroids. Liggins and Howie (Paediatrics 50 515 (1972)) produced data in humans which indicated that the risk of developing RI reduced by maternal injection of 12mg betamethasone c 2 days. There was no indication of obvious adverse e mother or foetus. The trial proposed here is to conf clinical findings as well as to investigate more form likely adverse effects.

Appendix 5. Dash provided protocol. Coded form NOT included. Dash coves in alphabetical coves.

SELECTION OF PATIENTS

The patient's consent to participate in the trial should be sought according to the policy of the hospital. Patients will be classified into two main groups:-

GROUP I Women at less than 34 weeks gestation (ie end of 33rd week) who are in clinical spontaneous premature labour either:

a) With ruptured membranes

or b) Without ruptured membranes

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RATIONALE

There is evidence from animal studies that surfactant is secreted into the foetal lungs if stimulated by corticosteroids. Liggins and Howie (Paediatrics 50 515 (1972)) produced data in humans which indicated that the risk of developing RDS was reduced by maternal injection of 12mg betamethasone daily for 2 days. There was no indication of obvious adverse effects to mother or foetus. The trial proposed here is to confirm these clinical findings as well as to investigate more formally any likely adverse effects.

SELECTION OF PATIENTS

The patient's consent to participate in the trial should be sought according to the policy of the hospital. Patients will be classified into two main groups:-

GROUP I Women at less than 34 weeks gestation (ie end of 33rd week) who are in clinical spontaneous premature labour

either:

a) With ruptured membranes

or b) Without ruptured membranes

GROUP II Women at less than 34 weeks gestation (ie end of 33rd week) who are not in premature labour but:

a) For whom early elective induction is indicated, and who show low lecithin concentrations or L/S ratios

b) For whom early elective induction is indicated but for whom no data is available on lecithin concentrations or L/S ratios

EXCLUSIONS FROM STUDY

1) Patients in whom steroid treatment is contra-indicated.

2) Patients for whom a delay of > 24 hours before delivery is not in the interest of mother or foetus.

3) Diabetics.

4) Amnionitis. (If amnionitis is diagnosed after admission of patient to the trial an indication of how the diagnosis was made should be recorded. Further trial data for such a patient should still be recorded.)

PATIENT NUMBER

During the year results will be subject to periodic review and the total number of patients to be included will depend on the significance of these results.

DESIGN OF TRIAL

Double-blind trial comparing intramuscular doses of 'Betnesol' with placebo.

DRUGS AND DOSAGE

Intramuscular injections of 'Betnesol' or matching placebo will be administered in a dosage of 1ml (= 4mg betamethasone 21 phosphate) every 8 hours over a 48 hour period (total of 6 doses). Only one course of 'Betnesol' or placebo treatment may be given.

Allocation of patients to either placebo or active groups will be done according to a random code. The ampoules will be provided in numbered boxes to facilitate this.

PROCEDURE

1) Patients will be examined on admission. Each patient will be allocated a trial number, a data sheet and a box of ampoules bearing her trial number.
2) Relevant patient details will be noted on the data sheet.
3) GROUP I
   a) Inhibition of uterine contractions will be attempted using salbutamol according to a standard scheme, (see Appendix I). If possible labour will be delayed for at least 48 hours. If delivery occurs in less than 48 hours all data should still be recorded.
   b) Each patient will receive an intramuscular injection of 'Betnesol' (4mg) or placebo according to a random code.
   c) 'Betnesol' injection (4mg) or placebo will then be administered at 8 hourly intervals over a period of 48 hours.
   d) Antibiotics will not be routinely administered in cases of spontaneous ruptured membranes.

e) If the patient goes into premature labour again after the 6th (last) injection of 'Betnesol' (or placebo) salbutamol may be re-used at the discretion of the physician, but on no account should further 'Betnesol' or placebo be given.

4) GROUP II a)

i) In these patients amniocentesis will be carried out. Those who show a low lecithin concentration or L/S ratio according to the standards of each hospital, will receive an intramuscular injection of 'Betnesol' (4mg) or placebo. This will be repeated at 8 hourly intervals over a 48 hour period (6 injections). The standards for interpreting the amniocentesis results should be defined at the beginning of the trial.

ii) 48 hours after the start of the treatment period (or as soon as possible thereafter) amniocentesis will again be carried out to determine the lecithin concentration or L/S ratio.

5) GROUP II b)

i) Amniocentesis is not applicable for these patients, therefore no data on L/S ratios or lecithin concentrations will be available. The patients will receive an intramuscular injection of 'Betnesol' (4mg) or placebo every 8 hours for 6 injections.

6) GROUPS I, II a) and II b)

i) The clinician will decide clinically on the optimum time interval between completion of steroid treatment and delivery (ideally between 48 hours and 7 days after the start of 'Betnesol' or placebo treatment).

ii) Maturity will be assessed 24-48 hours after birth in a well baby; this assessment may be postponed in a baby who is very ill. Signs of hyaline membrane disease, as listed on the record form, will be noted. In the case of post-mortem, tissues should be retained for inclusion body counts which will be performed centrally.

iii) Adrenal function of baby. Approximately 5ml of cord blood from the umbilical vein should be collected immediately after the end of the third stage of labour, preferably by syringe and needle, and placed in a heparinized bottle. It taken at night, whole blood may be stored in a fridge ($4^{o}C$). All samples should subsequently be centrifuged and the plasma deep frozen ($-20^{o}C$). Plasma 17-hydroxycorticosteroids will be estimated centrally or in the individual hospitals depending on the facilities available.

iv) In some centres adrenal function of mothers will be monitored for several days following delivery (method to be decided).

WITHDRAWALS

Any patient may be withdrawn from the trial at the discretion of the clinician. A reason for withdrawal should be stated on the data sheet.

SIDE EFFECTS

Any side effects attributed to the treatments used in this trial should be notified to Glaxo Laboratories immediately. This is a requirement of the Committee on Safety of Medicines.

In the event of any queries please contact:-

Dr C H Dash/Mrs B M Mullinger, Medical Department
Glaxo Laboratories Ltd, Greenford, Middlesex.
Tel: 01-422 3434 Ext 363

Appendix I: Use of salbutamol in Group I patients for the management of premature labour

(for trial of corticosteroids in the treatment of RDS)

Patients: All patients in Group I presenting in spontaneous premature labour without evidence of amnionitis. thyrotoxicosis or cardiac disease. The physician should be satisfied that premature labour has commenced, ie. regular contractions occurring at intervals of 10 minutes or less. Salbutamol treatment will then be started immediately.

Assessment before Salbutamol Treatment: Cervical dilatation and effacement will be recorded on the record form together with maternal blood pressure, pulse rate and foetal heart rate.

Composition of Salbutamol Infusion: 5ml = 5mg salbutamol injection should be added to 500ml 5% dextrose solution to give a concentration of 10µg salbutamol per ml equivalent to 15 drops from a normal giving set.

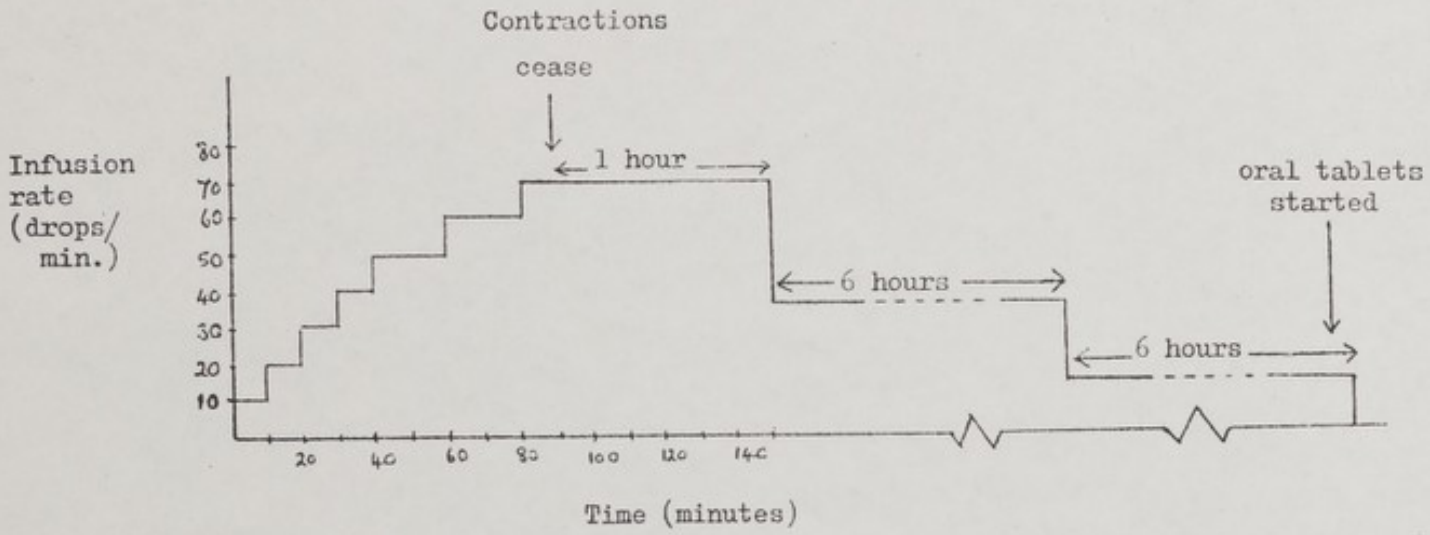
Treatment: Patients will receive an infusion of salbutamol through a forearm vein. The infusion will be started at 10 drops per minute (6.7 µg salbutamol/minute) and increased by 10 drop increments at five to ten minute intervals until contractions cease or an infusion rate of 50 drops per minute (33 µg/min) is reached. If contractions have not ceased, the infusion will be increased by 10 drop increments at 20 minute intervals. Treatment should be stopped if any of the following occur:

1. An infusion rate of 80 drops per minute (53 µg per minute salbutamol) does not reduce contractions in strength, duration or frequency.
2. The cervix has dilated significantly after six hours of treatment.
3. A steady maternal pulse rate exceeding 140/min is reached.

Once contractions have ceased, the infusion will be maintained at this steady rate for one hour. The infusion rate will then be reduced by half and maintained at this lower rate for six hours. The infusion rate will then be reduced by half again and maintained for a further six hours, before starting oral treatment with 4mg salbutamol (Ventolin) tablets qds for 1 week.

In the event of unacceptable side effects occurring such as tremor or palpitations, salbutamol dosage by infusion or oral routes may be reduced.

Example of Salbutamol Treatment



Records: Uterine contractions, maternal pulse rate and blood pressure and foetal heart rate will be monitored regularly (or prior to each change in salbutamol dose), until the maintenance infusion rate is reached; thereafter records will be made at 30 minute intervals until infusion is stopped.

Repeat therapy: If contractions become re-established during or after infusion treatment, the infusion will be increased or re-started at the previous 1 hour maintenance level and reduced as before at six hourly intervals.

Treatment will not normally be repeated on more than four occasions or after thirty-six weeks gestation without the direction of the clinician concerned.

Specific queries regarding the use of salbutamol may be addressed to:-

Miss Stephanie Marsh
Clinical Research Unit
Allen and Hanburys Research Ltd
Ware
Herts

Tel: Ware 3232 Ext 286

004 039

ON ADMISSION - TO BE FILLED IN BY HOUSE OFFICER ON ADMISSION

(Tick boxes where appropriate - do not fill in shaded boxes. For numerical data fill in as follows e.g. Treatment number 86 = 0086.)

A

HOSPITAL | AGE | TREATMENT NUMBER (i.e. THAT ON THE DRUGS) | Rx CODE | SMOKING HABITS DURING PREGNANCY (Approx. no. per day)

MENSES / LMP (date) Regular ☐ Irregular ☐ | GESTATION (from LMP) ☐☐ wks+ ☐☐ days | IS PATIENT CERTAIN OF DATES (±5 days)? Yes ☐ No ☐

OBSTETRICIAN'S ASSESSMENT OF GESTATION

Is assessment in keeping with above estimation of gestation? Yes ☐ No ☐

If No, what is obstetrician's assessment? ☐☐ weeks

PREVIOUS OBSTETRIC HISTORY

Gravid ☐☐

Parous ☐☐

HISTORY OF ORAL CONTRACEPTIVE USE

Months on o/c before present pregnancy ☐☐ m

Months stopped o/c before pregnancy ☐☐ m

Combined o/c ☐ Progestogen only ☐

DRUG	FROM (WEEKS GESTATION)	TO (WEEKS GESTATION)	DOSE	INDICATION	CODE (do not fill in this column)
1					☐☐☐
2					☐☐☐
3					☐☐☐
4					☐☐☐
5					☐☐☐

TO BE FILLED IN BY HOUSE OFFICER ON ADMISSION

B

HYPERTENSION (highest value during pregnancy) systolic bp ☐☐☐ diastolic bp ☐☐☐

ALBUMINURIA Present ☐ Absent ☐

If present is this due to urinary infection? Yes ☐ No ☐

CLINICAL OEDEMA Present ☐ Absent ☐

TOTAL WEIGHT GAIN DURING PREGNANCY ☐☐.☐ kg

ANTEPARTUM HAEMORRHAGE (if present) Yes ☐ No ☐ Not investigated ☐

Placenta praevia ☐ Abruptio placentae ☐ Unknown ☐

ANY OTHER COMPLICATIONS OF PREGNANCY (list)

PD3600/5

C IS PATIENT IN PREMATURE LABOUR? (If No, proceed to Group II patients) Yes [19] No [20] 004 039

GROUP I PATIENTS

MEMBRANES	DEGREE OF EFFACEMENT	CERVICAL DILATION
Ruptured [21]	(% or NK if not known) [23][24]	(cm or NK if not known) [25][26]
Intact [22]		
Uncertain [27]		

FACTORS PREDISPOSING TO PREMATURE LABOUR — DETAILS

	Yes	No
a) Recent operative procedure	[28]	[29]
b) Urinary tract infection	[30]	[31]
c) Other infection	[32]	[33]
d) Multiple pregnancy	[34]	[35]
e) Trauma	[36]	[37]
f) APH	[38]	[39]
g) Incompetent cervix	[40]	[41]
h) Abnormal uterus	[42]	[43]
i) Rhesus incompatibility	[44]	[45]
j) Other (specify) _____	[46]	[47]

PLEASE FILL IN SALBUTAMOL RECORD FORM ATTACHED

GROUP II PATIENTS

IS THIS A PLANNED DELIVERY? Yes [49] No [50]

IF SO, REASON
- Toxaemia [48]
- Rhesus incompatibility [51]
- Other (specify) _____ [52]

INITIAL LECITHIN/SPHINGOMYELIN AREA RATIO OR LECITHIN CONCENTRATION (if available)
- Normal [53]
- Abnormally low [54]
- Doubtful [61]

Date [55][56] Day [57][58] Month [59][60] Year

PD3600/5

SALBUTAMOL RECORD FORM – GROUP I PATIENTS

1

(To be completed at time of observation)

INITIAL ASSESSMENT NAME: TREATMENT NO. (As section A, page 1) ☐☐☐☐

CONTRACTION RATE/10 MINS ☐☐ FORCE: weak ☐ medium ☐ strong ☐

CERVICAL EFFACEMENT: nil ☐ partial ☐ complete ☐ CERVICAL DILATION ☐☐ cms

MEMBRANES: intact ☐ ruptured ☐ If ruptured, Date:-_____ Time:-_____

INITIAL MATERNAL BP s ☐☐☐ d ☐☐☐ PULSE RATE ☐☐☐/min FOETAL HEART RATE ☐☐☐/min

SALBUTAMOL INFUSION RECORDS Date started:-_____ Time:-_____

TIME (mins)	INFUSION RATE	MATERNAL BP	MATERNAL PULSE RATE	FHR	UTERINE CONTRACTIONS DURATION (secs)	UTERINE CONTRACTIONS RATE/ 10 MINS	OTHER DRUG TREATMENT OR SIDE EFFECTS

Continued on next page

SALBUTAMOL RECORD FORM 2

DATE AND TIME (mins)	INFUSION RATE	MATERNAL		FHR	UTERINE CONTRACTIONS		OTHER DRUG TREATMENT OR SIDE EFFECTS
		BP	PULSE RATE		DURATION (secs)	RATE/ 10 MINS	

INFUSION STOPPED Date:-_____ Time:-_____

SALBUTAMOL TABS. 4mg q.d.s. STARTED Date:-_____ Time:-_____

ANY CHANGE IN DOSAGE?

LABOUR RE-ESTABLISHED Date:-_____ Time:-_____

REPEAT TREATMENT GIVEN Yes ☐ No ☐

If Yes, please fill in continuation form (next page)

CONTINUATION FORM FOR REPEAT OF SALBUTAMOL TREATMENT 3

(To be completed at time of observation)

CONTRACTION RATE/10 MINS ☐☐ FORCE: weak ☐ medium ☐ strong ☐

CERVICAL EFFACEMENT: nil ☐ partial ☐ complete ☐ CERVICAL DILATION ☐☐ cms

MEMBRANES: intact ☐ ruptured ☐ If ruptured, Date:-_____ Time:-_____

DATE AND TIME	INFUSION RATE	MATERNAL		FHR	UTERINE CONTRACTIONS		OTHER DRUG TREATMENT OR SIDE EFFECTS
		BP	PULSE RATE		DURATION (secs)	RATE/ 10 MINS	

FILL IN ONE RECORD FORM FOR EACH BABY WHEN MULTIPLE BIRTH. 004/
(Tick boxes where appropriate - do not fill in shaded boxes.)

F MOTHER'S TREATMENT NUMBER (see Mother's data sheet) [19][20][21][22] Rx CODE [23]

SINGLETON, TWIN, TRIPLET etc. (enter 1, 2, 3 etc.) [24]

ORDER OF BIRTH (if multiple pregnancy) 1st [25] 2nd [26] 3rd [27] 4th [28]

SEX M [29] F [30]

LIVE BIRTH [31] STILL BIRTH [32]

BIRTH WEIGHT [33][34][35][36] gms

APGAR SCORE 1 min after birth [37][38] 5 mins after birth [39][40]

TIME AFTER BIRTH OF CORD CLAMPING <1 min [43] >1 min [44]

TIME OF FIRST GASP [41] secs OR [42] mins

TIME OF REGULAR RESPIRATION [45][46] mins

RESUSCITATION Mucus extraction [47] IPPV [48]

Sodium Bicarbonate [49] Other (specify) [50] _____

Central cyanosis on arrival at baby nursery Present [51] Absent [52]

Time after delivery of arrival at nursery [53][54][55] mins

Temperature on arrival at nursery [56][57]:[58] °C

EVIDENCE OF INTRAUTERINE INFECTION

Clinical Positive [59] Negative [60]

pneumonia [61]

meningitis [62]

urinary infection [66]

other (specify) [70] _____

	POS.	NEG.	NOT DONE
Nasal swab culture	[63]	[64]	[65]
Ear swab culture	[67]	[68]	[69]
Gastric apirate	[71]	[72]	[73]

HYPOGLYCAEMIA (Blood Glucose < 20mg%)

G Routine Dextrostix Normal [19] Below 25 [20]

Lowest blood glucose = [21][22]:[23] mg% OR [24]:[25][26] mM/L at [27][28] hrs after birth

[29][30]:[31] mg% OR [32]:[33][34] mM/L at [35][36] hrs after birth

Duration of blood glucose < 20mg% = [37][38] hours

PD3600/6

JAUNDICE

H

Absent [19]

Present [21]

Highest serum bilirubin at [20] days after birth

= [22][23][24] mg% OR [25][26][27] µM/L

DETECTION OF HMD (between 4-24 hours after birth)

	PRESENT	ABSENT	TIME OF ASSESSMENT (hrs after birth)	DURATION OF SYMPTOMS (hrs)
Flaring nostrils	[28]	[29]	[30][31]	[32][33]
Grunting	[35]	[36]	[37][38]	[39][40]
Cyanosis	[42]	[43]	[44][45]	[46][47]
Rib retraction	[49]	[50]	[51][52]	[53][54]

Chest X-ray, 4-24 hours after birth

(for suspected HMD babies)

is consistent with HMD [34]

is not consistent with HMD [41]

uncertain [48]

Maximum tachypnoea = [55][56] per min at [57][58] hours

Is it possible that any ~~non-respiratory~~ other disease is responsible for these signs?

Yes [59] No [60] If Yes, specify _____

IF HMD PRESENT

I

Mild - never needed >40% O_2 [19]

Moderate - needed >40% but <80% O_2 [21]

Severe - needed >80% O_2 and/or IPPV [23]

IPPV [20]

CPAP [22]

Other [24] State _____

BLOOD GASES

Time (hours after birth)	pO_2	pCO_2	pH	Inspired O_2 concentration

Lois Reynolds

From: Clive Dash [Clive.Dash@bpl.co.uk]
Sent: 03 October 2005 17:33
To: ucgarey@ucl.ac.uk
Cc: l.reynolds@ucl.ac.uk
Subject: RE: Witness Seminar transcript

[virus checked]
Dear Lois
I have received back the protocol etc.
Please cite permission from myself.
Kind regards
Clive
=

DASH
(unable to attend)

++++++++++++++++++
Visit BPL's Website
www.bpl.co.uk
++++++++++++++++++

BPL is part of NHS Blood and Transplant
++

Lois Reynolds

From: Clive Dash [Clive.Dash@bpl.co.uk]
Sent: 03 October 2005 17:33
To: ucgarey@ucl.ac.uk
Cc: l.reynolds@ucl.ac.uk
Subject: RE: Witness Seminar transcript

[virus checked]
Dear Lois
I have received back the protocol etc.
Please cite permission from myself.
Kind regards
Clive
=

Witness Seminar: Prenatal Corticosteroids for reducing Morbidity and Mortality

The UK multicentre study[1] was designed in 1974, largely stimulated by the publication of Liggins & Howie[2] and their prior animal studies. The idea for a UK study was an amalgam of interest from some obstetricians and neonatal paediatricians and from within Medical Dept of Glaxo in the UK because of the organizational link with the antipodes.

Clinicians' views can change during the planning and conduct of long-term studies (about 4 years to plan and complete recruitment and follow-up for the UK study[1]). All clinicians, who were involved in the early planning, recognized that more clinical work was needed to confirm the results from NZ[1]. Everyone involved in the study planning recognized that it was important to have commitment from an obstetrician and paediatrician at each participating hospital*. By the time the study recruitment started (about 1 year later), some of the clinicians did not wish to recruit patients to the study for various reasons, even after Ethics Committee approval. [Pertinent p. 28]
[* Pertinent p. 40]

At the time when Ross Howie presented the results to RCOG in 1977, the UK study was in its recruitment phase. Whether knowledge of the status of the UK study played any part in the cool response of the delegates at the meeting, which Ross sensed, would be speculative. [Pertinent pp.13, 38]

The response by the delegates at the RCOG meeting in 1977 may also have been tempered by the anxiety, certainly among many clinicians with whom I spoke at that time, that the long-term effects might prove to be significant. [Pertinent p. 104]

Because of the Glaxo link, it was well-known in the UK which product had been used in NZ[1]. The NZ product was an ester of betamethasone (acetate), the properties of which caused a slower absorption from the intramusclular site than the very soluble product (phosphate salt) available in the UK. It was estimated that more frequent injections of the soluble product would give a similar bio-availability. The placebo used in the UK was specially prepared for the study by Glaxo and consisted of the vehicle in which the phosphate salt was formulated. Both were clear solutions in identical vials and labeled similarly except for patient numbers assigned randomly. Thus, the blind was preserved. [Pertinent p.15]

I had the pleasure to meet Mont Liggins on one of his visits to the UK during the early planning of the UK study[1]. As others have said in this Witness Meeting, he was open with his results and encouraging us to do more. [Pertinent pp. 12/14/29/30]

A taxing question in the design and analysis of the UK study was the imprecision in estimating gestational age at the time of recruitment. Maternal dates and obstetrical palpation were the only antenatal assessments available then – so different from the current techniques! The clinicians documented both estimates for the analysis. These were augmented (or confounded) by neonatal assessment[3,4], which was also recorded.

[Pertinent p.21 *this change in clinical assessment is not mentioned in the transcript, but it is important to remind readers of the circumstances that were present when a particular piece of work was undertaken, by contrast to current times*]

In the mid-1970s in the UK, informed consent for clinical trials was generally verbal. It was later that written consent and now written informed consent became part of normal practice. [Pertinent p. 19]

The UK study was being planned at the time of the move from ethanol as a tocolytic to various newly introduced beta-agonists. We decided to use salbutamol, if a tocolytic was clinically necessary, so as to standardize one of the management modalities – and also because salbutamol was developed by Glaxo! [Pertinent p. 30/31]

The UK study[1] finished recruitment in early 1978 and the findings of the initial analysis supported those that had been reported reported elsewhere. These included a mortality benefit especially in infants born before 34 weeks gestation; within 8 days after the mother had entered the study; and if the mother had received at least three injections of betamethasone phosphate (12mg). No new or interesting results were found. Partly because of this, I did not think that publication of the study was a worthwhile priority (insufficiently newsworthy). However, due to the persuasive powers of the late, Harold Gamsu (for whom I have great admiration for his pleasant persistence and continuous striving to fully understand the data) I was persuaded to coordinate a more detailed analysis of the data with other colleagues at Glaxo.

[Pertinent pp. 30, 43]

In the planning of the UK study[1], we discussed whether a single course of betamethasone or, if necessary, repeat courses at weekly intervals was appropriate. We decided on a single course, partly because of worries about safety in the short- and long-term and partly because of the logistics of providing the same blinded medication for each patient.

[Pertinent pp. 35/101]

In the UK study[1], only 20% of the recruited patients delivered between 24 hours and one week after recruitment (25% before 24 hours and 55% after one week).

[Pertinent p. 52]

The retention of clinical trial data in the 1970/80s was poor. This has changed in recent years. When Harold Gamsu persuaded us to do a detailed analysis of the UK study, the computer software had changed and so had most personnel acquainted with the prior system. Luckily, Alex Paton at Glaxo was able to interrogate the database and through her efforts we were able to meet Harold's expectations and answer his critical questions. Also, Harold volunteered to keep safe the original case record forms and other study documentation when Brenda Mullinger and I left Glaxo to pursue other career opportunities. I believe Harold always hoped to trace the babies in adult life to address the question of the long-term safety. It is due to his diligence and enthusiasm that he persuaded us (again, pleasantly) in 2001 to begin the process towards a 30+ years follow-

up. His untimely death occurred in August 2004, soon after this Witness Meeting. We hope to continue this project with the support of NPEU in Oxford provided external support can be mobilized and plan to dedicate any outcomes to his memory.
[Pertinent p. 54/55]

Various preparations of betamethasone are available in different countries. The preparations are all designed to release the active sterol, betamethasone, but at different rates. The soluble phosphate preparation is suitable for intravenous administration, like hydrocortisone, as well as intramuscular injection. The acetate preparation is not suitable for IV use. Some products are a mixture of the acetate and phosphate derivatives (*e.g.*Celestone®, Schering). [Pertinent p. 105]

In some countries dexamethasone is more readily available than betamethasone and this is why it has featured in some studies. These two steroids are isomers in which the methyl group differs in its orientation (dexamethasone is 9–*alpha*-fluoro 16-*alpha* methyl prednisolone; betamethasone is 9-*alpha*-fluoro 16-*beta* methyl prednisolone)[5]. In the usual pharmacological tests of corticosteroid potency, they are equivalent. In general, the mode of action (pharmacodynamics) seem similar, so they should be therapeutically equivalent. [Pertinent p. 105]

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2. Liggins G C, Howie R N. *Pediatrics* 1972; 50: 515-525.
3. Farr V, Mitchell R G, Neligan G A, Parkin J M. *Dev Med Child Neurol* 1966; 8: 507-511.
4. Dubowitz L M, Dubowitz V, Goldberg C. *J Pediatr* 1970; 77: 1-10.
5. Sweetman S C (Ed) Martindale 33rd Ed. Pharmaceutical Press, London 2002; 1063 & 1067.

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19th March 2004

Dear Dr Davies

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004
2.00 pm – 6.00 pm

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is organising a Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15th June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1 2BE. Dr Edmund Hey has kindly agreed to chair the meeting and Sir Iain Chalmers is assisting us in the organisation.

Sir Iain Chalmers has recommended that we invite you to this meeting and we would be delighted to have you join us.

As you know, these seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history. I enclose a flyer of our recent publications to illustrate the range of topics we cover.

Continued/... Page 2

We are in the process of inviting senior scientists, clinicians, and representatives from relevant organisations to attend the meeting and hope to promote a lively discussion.

We will be providing further details in due course and would particularly appreciate, at this stage, suggestions of possible participants.

I look forward to hearing from you and do hope you will be able to accept this invitation.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

1614104

Tel: 020 7289 8207

22 Manor House Court
11 Warrington Gardens
London
W9 2PZ

7th April 2004

Dr. Daphne Christie
The Wellcome Trust Centre for the
History of Medicine
24 Eversholt Street
London NW1 1AD

Dear Dr Christie

Your letter of 19th March addressed to me at The Garden Flat, 22 Warrington Crescent, reached me today. (I have been at the above address for nearly 4 years).

While I greatly appreciate the invitation to take part in the Writers Seminar on 15th June I am going to refuse because I do not believe I could contribute usefully to it. Although my memory for past events is better than most for recent events, I cannot guarantee accuracy of either and have a horror of participating. I do hope you + Sir Iain will understand

Yours sincerely
Pamela A Davies

P.A. DAVIES

The Wellcome Trust Centre for the History of Medicine at University College London

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UCL

Prof Sir Liam Donaldson
Chief Medical Officer Richmond House
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11 March 2004

Sir Liam

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004
2.00 pm – 6.00 pm

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is organising a Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15th June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1. Dr Edmund Hey has kindly agreed to chair the meeting and Sir Iain Chalmers is assisting us in the organisation.

Sir Iain Chalmers has recommended that we invite you to this meeting and we would be delighted to have you join us.

These seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history. I enclose a copy of the introduction to the first volume of our published transcripts, which will tell you a little more about these seminars, and a flyer of our recent publications to illustrate the range of topics we cover.

Continued/... Page 2

The Wellcome Trust Centre for the History of Medicine at University College London is funded by the Wellcome Trust, which is a registered charity, no. 210183. Histmed logo images courtesy *Wellcome Library*, London.

We are in the process of inviting senior scientists, clinicians, and representatives from relevant organisations to attend the meeting and hope to promote a lively discussion. We will be providing further details in due course and would particularly appreciate, at this stage, suggestions of possible participants.

I look forward to hearing from you and do hope you will be able to accept this invitation.

Yours sincerely

Daphne Christie

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 23 March 2004 08:52
To: Katy.Dyer
Cc: Wendy
Subject: RE: Witness Seminar - Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth - 15 June 2004

Dear Miss Dyer
Thank you for your e-mail. We are sorry that Sir Liam is unable to attend the witness seminar on Tuesday 15 June.
Yours sincerely
Daphne Christie

-----Original Message-----
From: Katy.Dyer@doh.gsi.gov.uk [mailto:Katy.Dyer@doh.gsi.gov.uk]
Sent: 19 March 2004 15:49
To: d.christie@ucl.ac.uk
Subject: Witness Seminar - Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth - 15 June 2004

Our ref: INV212/2004

Dear Dr Christie

Sir Liam Donaldson has asked me to thank you for your letter dated 11 March inviting him to attend the above event.

Unfortunately, Sir Liam is unable to accept your kind invitation due to an existing commitment on that date.

Yours sincerely

Katy Dyer
Diary Secretary
Tel: 0207 210 5152
Fax: 0207 210 5407

Professor James Drife FRCS FRCOG
Division of Obstetrics & Gynaecology
University of Leeds School of Medicine
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19th March 2004

Dear Professor Drife

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004
2.00 pm – 6.00 pm

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is organising a Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15th June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1 2BE. Dr Edmund Hey has kindly agreed to chair the meeting and Sir Iain Chalmers is assisting us in the organisation.

Sir Iain Chalmers has recommended that we invite you to this meeting and we would be delighted to have you join us.

As you know, these seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history. I enclose a flyer of our recent publications to illustrate the range of topics we cover.

Continued/... Page 2

We are in the process of inviting senior scientists, clinicians, and representatives from relevant organisations to attend the meeting and hope to promote a lively discussion.

We will be providing further details in due course and would particularly appreciate, at this stage, suggestions of possible participants.

I look forward to hearing from you and do hope you will be able to accept this invitation.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

Academic Unit of Paediatrics
and Obstetrics and Gynaecology

From the Division of Obstetrics and Gynaecology

D Floor, Clarendon Wing (LGI)
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Leeds LS2 9NS

Telephone: +44 (0)113 243 2799
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Dr Daphne Christie,
Senior Research Assistant to Dr Tilli Tansey,
The Wellcome Trust Centre for the History of Medicine
at University College London,
24 Eversholt Street,
London NW1 1AD

20th March 2004

Dear Dr Christie,

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004
2.00pm – 6.00pm

Thank you very much for your letter of 19th March, kindly inviting me to take part in this Witness Seminar. I have happy memories of taking part in a previous Witness Seminar and I am very flattered that Sir Iain Chalmers has suggested inviting me to this one. I am delighted to accept your invitation.

I have clear memories of perplexed clinical discussions during the 1980s about the advisability or otherwise of using prenatal corticosteroids, while we were still relying on the evidence of individual trials. I hope these recollections may be of interest and I hope that we shall also reflect on the general change in approach to evidence-based medicine that followed the introduction of new methods of addressing this problem.

I am very much looking forward to the seminar, and thank you again for inviting me.

Best wishes,

Yours sincerely,

James Drife, MD FRCOG FRCPE FRCSE
Professor of obstetrics and gynaecology

The Wellcome Trust Centre for the History of Medicine at University College London

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26 April 2004

Dear Professor Drife

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004, 2pm–6pm

We are delighted that you are able to attend the above meeting and are happy to tell you that plans are proceeding well. A copy of our publicity material is enclosed and I will be sending you a draft programme in due course. A full attendance list will be available at the meeting.

We will be asking some participants to "start the ball rolling" by saying a few words on specific subjects, as we like to prime a few people to lead off the discussions, although there will be ample opportunity to contribute throughout the meeting. We do not show slides or overheads at the meetings, as we wish to encourage informal interchange and conversation. If however, you would like any material to be available to the audience, we could photocopy a diagram or article for you, and leave a copy on every chair.

Please do not hesitate to contact either myself or Mrs Wendy Kutner 020 7679 8106 if you have any queries prior to the meeting.

We very much look forward to seeing you at the meeting.

Yours sincerely

pp **Dr Daphne Christie**
Senior Research Assistant to Dr Tilli Tansey

enc.

The Wellcome Trust Centre for the History of Medicine at University College London is funded by the Wellcome Trust, which is a registered charity, no. 210183. Histmed logo images courtesy *Wellcome Library*, London.

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 11 June 2004 10:00
To: Wendy
Subject: Tuesday james drife

Importance: High

James Drife called to say that unfortunately he won't be able to attend on Tuesday due to an urgent request for him to be in Brighton that day. He will contact Iain and give his apologies.
Thanks, Daphne

Dr Daphne Christie
History of Twentieth Century Medicine Group
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Dr Daphne Christie

From: James Drife [J.O.Drife@leeds.ac.uk]
Sent: 14 June 2004 00:37
To: shey
Cc: ichalmers
Subject: Witness seminar

Dear Dr Hey,
I have been in touch with Iain Chalmers and Daphne Christie to let them know that unfortunately the GMC has interfered in a major way with my plan to come to the seminar on Tuesday. I am part of the team of inspectors of the new Brighton/Sussex Medical School, and I thought I had managed to arrange things so that other team members inspected the School's first-ever end-of-year OSCE examinations on Tuesday. Unfortunately one of the other team members has had to withdraw, and there is nobody apart from myself to take his place. I am very disappointed not to be able to join you at the Seminar. I have taken part in one before and I found it very interesting and enjoyable. I'm sure this one will be too.

Iain suggested that I should let you know what I would have said at the seminar. Here is my two pen'orth.

I can clearly date some of my medical experiences because I've moved between various centres in the UK over the past thirty years. Between 1982 and 1990 I worked in Leicester as a senior lecturer in obstetrics and gynaecology. (The head of department was Professor John Macvicar, who has his place in history as the co-author with Ian Donald of the first paper on obstetric ultrasound.) Leicester Royal Infirmary had the neonatal intensive care unit for the area, and as well as our own patients we would receive women transferred from elsewhere in threatened preterm labour. Obstetric opinion about the use of antenatal steroids was not so much divided as perplexed, with all of us aware that the published literature at the time lacked consensus. Nor was there any background of traditional practice to guide us. We sought the opinion of the neonatal paediatricians, in particular Dr Malcolm Levene, who coincidentally is now Professor of Paediatrics in Leeds, in the same hospital as myself. Malcolm specialised in neonatal care (and has written textbooks on it) and he normally enjoyed the opportunity to give advice to his obstetric colleagues, though he always acknowledged that balancing the interests of mother and baby was no easy matter. He would gallantly say that it was much easier to be a paediatrician. We did not always take his advice but we certainly recognised that he was bang up to date with what was best for baby.

What sticks in my memory particularly was that Malcolm was as uncertain as we were about the use of antenatal steroids. He felt that on balance they were probably helpful for the baby but he recognised that there were conflicting views and he could not offer us clear guidance. We had similar conversations with him on several occasions, and to the best of my recollection the picture remained confused right up until the time that he left to take up his chair in Leeds in 1988.

Iain asked if I could remember when things changed, but I cannot date this accurately. I myself moved to Leeds in September 1990. The obstetric guidelines at the Leeds General Infirmary at that time were under the control of one of the NHS consultants and I could not say exactly when the routine use of steroids started here.

I do remember the temptation to use the wisdom of hindsight as soon as the picture had been clarified by the use of meta-analysis, but I would want to stress the difficulty that well-informed and highly motivated people had in interpreting the literature before this technique had been developed.

I hope this little bit of personal reminiscence may be of some use, and I'm sorry I won't be there to hear the rest of the story from the major players.

Best wishes,

Jim Drife

Wendy Kutner

From: Sheila Duncan [sheila.l.b.duncan@virgin.net]
Sent: 05 May 2004 20:50
To: Wendy Kutner
Subject: Witness Seminar

Dear Wendy,

I have received the circular about the Witness Seminar on Tuesday 15th June on "Prenatal corticosteroids ---
---".

I would be interested to attend.

Yours, Sheila Duncan

Professor Peter Dunn FRCP FRCOG FRCPCH
Emeritus Professor
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19th March 2004

Dear Peter

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004
2.00 pm – 6.00 pm

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Sir Iain Chalmers has recommended that we invite you to this meeting and we would be delighted to have you join us.

As you know, these seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history. I enclose a flyer of our recent publications to illustrate the range of topics we cover.

Continued/... Page 2

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We will be providing further details in due course and would particularly appreciate, at this stage, suggestions of possible participants.

I look forward to hearing from you and do hope you will be able to accept this invitation.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

Peter M Dunn, MA, MD, FRCP, FRCOG, FRCPCH
Emeritus Professor of Perinatal Medicine
and Child Health

Home Address

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173 Henbury Road
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Bristol
BS10 7AD
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Department of Child Health
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BS10 5NB
Tel: 0117 9505050 Ext. 3823

Our Ref: PMD/gmv
Date: 2nd April 2004

Dr. Daphne Christie
Senior Research Asst. to Dr. Tilli Tansey
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of Medicine
24 Eversholt Street
London
NW1 1AD

Dear Daphne,

Re: Witness Seminar – Prenatal Corticosteriods .....

It was very kind of Iain Chalmers, Ed Hey and yourself to invite me to this Wellcome Trust Seminar. I would really have enjoyed participation but unfortunately am not able to get away to London on that day. I look forward in due course to reading the transcripts when they are published.

Thank you again for inviting me.

Yours sincerely,

Peter M. Dunn

FFPHM RCP

Professor John Gabbay

John Gabbay, Professor of Public Health, is Director of the Wessex Institute for Health Research and Development. This chiefly comprises the NHS National Co-ordinating Centre for Health Technology Assessment (NCCHTA), and the Southampton HTA Centre (SHTAC).

Professor Gabbay's past research has focussed on the evaluation of organisational schemes to improve the quality of clinical care in the NHS. Other recent research has included a review of methods for early identification of emerging health technologies, and work on the use of population health indicators in the NHS. His early work was on the social construction of medical knowledge from a historical perspective, and he later carried research on management and organisational behaviour in the NHS.

He led the team which produced the report of the Clinical Standards Advisory Group on clinical effectiveness, using the care of stroke as the exemplar, and demonstrated that the then government's policies on improving the quality of clinical care were fundamentally flawed in their implementation. The recommendations from that report helped to influence the 1997 government White Paper, A First Class Service. He has also helped to evaluate other regional and national schemes including the Oxford Region GRiPP (Getting Research into Practice and Policy), the King's Fund/ Department of Health PACE (Promoting Action on Clinical Effectiveness) programmes, and the Welsh Clinical Effectiveness Initiative, highlighting some of the keys to success and failure. A forthcoming book commissioned by Oxford University Press on the organisational behavioural aspects of evidence-based health care will synthesise the results of these and three further related research projects carried out by Professor Gabbay and his co-authors.

A recent grant from the NHS Services Development and Organisation Programme - jointly with University College London - will allow him to study qualitatively the ways in which patient pathways are designed and implemented as part of the new NHS Diagnosis and Treatment Centres. This work links with his interest in the use of research knowledge to improve health services. As a member of the Treatment Decisions Group of the Community Clinical Sciences Research Division, his current work in this field also includes an action research project working with two "Communities of Practice" to understand the knowledge behaviours of multisectoral groups who are designing and implementing improvements in the care of the elderly, and an ethnographic study of knowledge management in primary care. He is also a member of the MRC Qualitative Depression Study, which will lead to a deeper understanding of treatment decisions for depressed patients in primary care.

Gabbay J, Dopson S, Ferlie E, Fitzgerald L, Locock L. Understanding the role of opinion leaders in putting evidence into practice: the methodological challenge of reviewing qualitative research: *Journal of Epidemiology & Community Health* Vol 54 No 10 October 2000 p 780. (abstract)

Recent Publications

Oliver S, Milne R, Bradburn J, Buchanan P, Kerridge L, Walley T, **Gabbay J.** Involving consumers in a needs-led research programme: a pilot project. Health Expectations 2001 Vol 4 No 1. March 2001

Oliver S, Milne R, Bradburn J, Buchanan P, Kerridge L, Wally T, **Gabbay J.** Investigating consumer perspectives on evaluating health technologies Evaluation: 2001 (4) 468 - 486

Robert G, Stevens A, **Gabbay J.** Identifying New Healthcare Technologies: Methods in Evidence Based Healthcare SAGE 2001 chapter 25, p 451

Dopson S, Locock L, Chambers D, **Gabbay J.** Implementation of evidence-based medicine: evaluation of the Promoting Action on Clinical Effectiveness programme. J Health Services Research and Policy 2001 Vol 6 No 1 23-31

Gabbay J, Kerridge L, Milne R, Stein K. The NHS R&D Health Technology Assessment programme. In Baker MR, Kirk S, eds. Research and Development for the NHS: evidence, evaluation and effectiveness , pp 141-62. Abingdon, Oxon.: Radcliffe Medical Press, 2001.

Ferlie E, **Gabbay J**, Fitzgerald L, Locock L, Dopson S. Evidence-based medicine and organisational change: An overview of some recent qualitative research. In Ashburner L, ed. Organisational behaviour and organisational studies in health care: Reflections on the future, pp 18-42. Palgrave, 2001.

Locock L., Dopson S., Chambers D, **Gabbay J.**. Understanding the role of opinion leaders in improving clinical effectiveness. Social Science and Medicine: 2001 53 (6): 745-757

No magic targets! Changing Clinical Practice to Become More Evidence Based. Health Care Management Review 2002 (27) 35 - 47

Surender R, Locock L, Chambers D, Dopson S, **Gabbay J:** Closing the Gap Between Research and Practice in Health: Lessons from a clinical effectiveness initiative Public Management Review: 2002 (4) 45 – 61

Exworthy M, Wilkinson E K, McColl A, Moore M, Roderick P, Smith H, **Gabbay J.** The role of performance indicators in changing the autonomy of the general practice profession in the UK, Social Science and Medicine: In Press, Uncorrected Proof, Available online 9 June 2002

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Tel: +44 (0) 2380 595649

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 03 March 2004 08:39
To: Wendy
Subject: FW: witness seminar prenatal corticosteroids 15 June

Please draft a letter to John Gabbay. Thanks, Daphne

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 02 March 2004 18:54
To: d.christie@ucl.ac.uk
Cc: Edmund Hey (E-mail)
Subject: RE: witness seminar prenatal corticosteroids 15 June

Dear Daphne, Excellent that Miranda can come. I'd be delighted if John Gabbay comes. Has Patricia Crowley responded. She's crucially important. I'll discuss other witnesses with Ed Hey and get back to you. Best wishes, Iain

-----Original Message-----
From: Dr Daphne Christie [mailto:d.christie@ucl.ac.uk]
Sent: 02 March 2004 10:55
To: Iain Chalmers
Subject: witness seminar prenatal corticosteroids 15 June

Dear Iain
This is just to let you know that Professor Miranda Mugford has replied to say that she is able to attend the witness meeting. She has suggested inviting Dr John Gabbay (University of Southampton)as a witness. Please confirm that you agree with this. I have sent you a copy of her letter. Please can we have some names of other witnesses. Wendy is back and can send invitations this week.
Thank you.
With best wishes,
Daphne

Dr Daphne Christie
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--

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Professor John Gabbay FFPHM RCP
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3 March 2004

Professor Gabbay

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004
2.00 pm – 6.00 pm

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is organising a Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15th June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1. Dr Edmund Hey has kindly agreed to chair the meeting and Sir Iain Chalmers is assisting us in the organisation.

Professor Miranda Mugford and Sir Iain Chalmers have both recommended that we invite you to this meeting and we would be delighted to have you join us.

These seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history. I enclose a copy of the introduction to the first volume of our published transcripts, which will tell you a little more about these seminars, and a flyer of our recent publications to illustrate the range of topics we cover.

Continued/... Page 2

We are in the process of inviting senior scientists, clinicians, and representatives from relevant organisations to attend the meeting and hope to promote a lively discussion. We will be providing further details in due course and would particularly appreciate, at this stage, suggestions of possible participants.

I look forward to hearing from you and do hope you will be able to accept this invitation.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 16 April 2004 09:34
To: Gale M.
Cc: Wendy
Subject: RE: Oral History Day - 15 June

We are pleased that Professor Gabbay is able to attend the meeting in June and will be sending further details in due course.
With best wishes
Daphne Christie

-----Original Message-----
From: Gale M. [mailto:M.Gale@soton.ac.uk]
Sent: 07 April 2004 17:01
To: d.christie
Subject: Oral History Day - 15 June

Dear Dr Christie

Professor Gabbay thanks you for your invitation and will be delighted to attend.

Margaret

Margaret Gale
Office Manager & PA to Professor John Gabbay
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Mailpoint 728
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UCL

Professor John Gabbay FFPHM RCP, University of Southampton,
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26 April 2004

Dear Professor Gabbay

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004, 2pm–6pm

We are delighted that you are able to attend the above meeting and are happy to tell you that plans are proceeding well. A copy of our publicity material is enclosed and I will be sending you a draft programme in due course. A full attendance list will be available at the meeting.

We will be asking some participants to "start the ball rolling" by saying a few words on specific subjects, as we like to prime a few people to lead off the discussions, although there will be ample opportunity to contribute throughout the meeting. We do not show slides or overheads at the meetings, as we wish to encourage informal interchange and conversation. If however, you would like any material to be available to the audience, we could photocopy a diagram or article for you, and leave a copy on every chair.

Please do not hesitate to contact either myself or Mrs Wendy Kutner 020 7679 8106 if you have any queries prior to the meeting.

We very much look forward to seeing you at the meeting.

Yours sincerely

pp **Dr Daphne Christie**
Senior Research Assistant to Dr Tilli Tansey

enc.

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Wendy Kutner

To: Gabbay J.
Cc: ucgachr@ucl.ac.uk
Subject: RE: Witness Seminar: Prenatal corticosteroids - 15 June 2004

Dear Professor Gabbay, Thank you for your e-mail. We are very pleased you are still able to attend. We will be sending out a draft programme shortly and look forward to seeing you at the meeting. Wendy Kutner

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
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for the History of Medicine at UCL
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LONDON NW1 1AD

Tel: 020 7679 8106
Fax: 020 7679 8193
w.kutner@ucl.ac.uk
www.ucl.ac.uk/histmed

-----Original Message-----
From: Gabbay J. [mailto:J.Gabbay@soton.ac.uk]
Sent: 08 May 2004 16:47
To: w.kutner
Subject: RE: Witness Seminar: Prenatal corticosteroids - 15 June 2004

I guess you will have gathered now that I can come after all. Sorry for the "wobble".

Jx

-----Original Message-----
From: Wendy Kutner [mailto:w.kutner@ucl.ac.uk]
Sent: 06 May 2004 15:23
To: J.Gabbay
Cc: Daphne Christie
Subject: Witness Seminar: Prenatal corticosteroids - 15 June 2004

Dear Professor Gabbay, Please find attached publicity flyer for the above meeting. Your name is still listed as attending! Please let Daphne or myself know whether you are able to attend, so I can leave your name there or remove it. It is fine to let me know nearer the meeting if that would be more convenient. We do hope you are able to attend. Wendy Kutner

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
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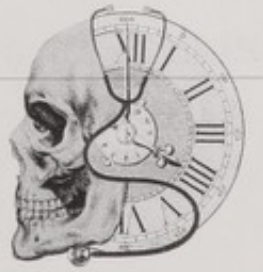

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16 June 2004

Dear Professor Gabbay

The Wellcome Trust History of Twentieth Century Medicine Group Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with pretern birth

May I say on behalf of The History of Twentieth Century Medicine Group and the co-organiser, how grateful we are to you for your contributions to yesterday's meeting? It really was a splendid occasion, and we hope that you enjoyed it as much as those of us who were observers.

As mentioned in previous correspondence and at the meeting, the taped proceedings of the meeting will now be sent for transcription, and we hope to have a draft manuscript to send you in about six months time for your comments. Ultimately we intend to publish an edited version of the proceedings, and you will be sent a copyright assignment form and final proof before publication.

Yours sincerely

Daphne Christie

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

Dr Daphne Christie

From: Gabbay J. [J.Gabbay@soton.ac.uk]
Sent: 10 January 2005 12:04
To: d.christie@ucl.ac.uk
Subject: RE: Witness seminar

To save you typing, and in case you want to tinker with it (feel free!) here is an electronic version of my bio.

John Gabbay, born 1949, qualified in medicine at Manchester in 1974. After 7 years at the University of Cambridge working on the social origins of medical knowledge, he trained in public health and in the 1980s carried out qualitative research on NHS management and clinical audit. >From 1992 to 2004, when he retired, he directed the Wessex Institute of Health R&D, which now houses the National Coordinating Centre for Health Technology Assessment, which he also directed. His recent research has focused on the implementation of evidence in clinical practice.

Jx

John Gabbay
Emeritus Professor, University of Southampton.
1 Daniells Close
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Office telephone: +44 (0) 2380 595649
Mobile: +44 (0) 7774 890016

Email: j.gabbay@soton.ac.uk <mailto:jg3@soton.ac.uk>

-----Original Message-----
From: Gabbay J.
Sent: 10 January 2005 11:38
To: 'd.christie@ucl.ac.uk'
Subject: Witness seminar

Just seen that you wanted the corrections and forms etc returned by today. I should be able to get them to you by Wednesday if that's OK. Rest assured I will have made only the slightest of changes to aid clarity!

Jx

John Gabbay
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Email: j.gabbay@soton.ac.uk <mailto:jg3@soton.ac.uk>

Do you know about http://www.thehungersite.com? When you click on the site, you generate the equivalent of 1.1 cups of staple food, funded by sponsors of this UN-generated scheme. You're allowed 1 click/day - that's around 400 cups/year of food aid - and there are easy links to other similar sites.

Lois Reynolds

To: J.Gabbay@soton.ac.uk
Subject: Witness Seminar: Corticosteroids, 15 June 2004

Dear Professor Gabbay,

I've taken over the editing of this transcript from Daphne Christie and notice that no corrections have been received since your email of 10 January 2005 with your biographical note.

I would be grateful for any changes that you wish to have included in the text.

Best wishes from Lois Reynolds

Mrs Lois Reynolds
Research Assistant to Dr Tilli Tansey
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email corticos 1/6/05

The Wessex Institute for Health Research & Development

The Wessex Institute for Health Research and Development

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Mobile: +44 (0) 7774 890016
Email: jg3@soton.ac.uk

recd 13.1.05
Ack "

2nd set of corrections recd 1/6/05

As promised by email. I look forward to the final product. J

With Compliments

University of Southampton

The Wellcome Trust Centre for the History of Medicine at University College London

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7 December 2004

Dear Professor Gabbay

Witness Seminar: Prenatal Corticosteroids for reducing Morbidity and Mortality

I enclose a draft transcript of the Witness Seminar on '**Prenatal Corticosteroids for reducing Morbidity and Mortality**' to which you contributed. We intend to publish a version of the transcript in November 2005 under the auspices of the Wellcome Trust Centre for the History of Medicine at UCL.

I would be most grateful if you could check your own contributions for general sense, accuracy and typographical mistakes. We do not encourage extensive alterations, as the purpose of these publications is to retain the freshness and informality of the meeting. However, any additional information can be added as a footnote and you may like to suggest such material Please mark all corrections clearly on this copy and return it to me by **Monday 10 January** Earlier published volumes in the series can be viewed on our website, www.ucl.ac.uk/histmed/witnesses.html

If you would like to comment on any other part of the transcript, other than the corrections to your own contribution, please feel free to do so.

- Please provide a 2–3 sentence biographical piece for inclusion in the notes at the end of the volume including year of birth and dates of major appointments. ✓
- Please sign and return the standard form assigning copyright to the Wellcome Trust. ✓
- Please let us know if you do not want your name included in our twice-yearly marketing mailings. Fine by me — but please note new address. 3/1/05
- We would like to include illustrations of early work in the volume. If you have any suitable images or figures, please include these with the pages. They will be carefully scanned and returned in protective packaging. None
- A final proof version, incorporating the changes made by all the participants, added footnotes, and any queries will be sent to you in **September 2005** for return within a week. **At this stage only minor corrections, such as those of a typographical nature, will be possible**.

The tapes, earlier versions of the transcript, and any additional correspondence generated by the editorial process, will be deposited in Wellcome Library. A version of the transcript will also be mounted on the Wellcome Trust Centre's website shortly after publication.

I look forward to hearing from you.

Yours sincerely

Daphne Christie

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

The Wellcome Trust Centre for the History of Medicine at University College London is funded by the Wellcome Trust, which is a registered charity, no. 210183. Histmed logo images courtesy *Wellcome Library*, London.

These are the only changes needed in my contributions JJ.

experience, counts at least, and of course what the great and the good around you are saying, your local opinion leaders, counts at least as much as what we would like people, as rational scientists, what we would like them to use as evidence. I would like to hear more about that interaction between different forms of evidence in people's minds as they develop their policies.

Mugford: I think it's just an anecdote to add to John's point, to the strength of it. When James Piercy and I went to the Department of Obstetrics in Oxford, at the end of his dissertation period, to present our economic modelling, Professor Turnbull was in the audience and he was very gracious and kind and very gentle with us as young researchers, but at the end of all the questions from midwives and neonatal nurses and house officers, he stood up and said but of course this is all, I cannot remember his exact words, and I won't even try to do it, but he very gently poured a lot of cold water on it, because we hadn't taken account of the effect on women, and the increase in risk of infection in women. And so I bowed to his authority, I couldn't deny it, but I said as far as I knew the systematic review had not shown any effect in that respect, but I wasn't confident enough. So that the general mood of the audience I think at the end was that the authority was that what we had done had been a bit of a waste of time.

Chalmers: Alex Turnbull was Professor of Obstetrics in Oxford at the time. He was also one of the people looking at the maternal mortality

experiences for the report and I know that he was very influenced by a particular woman who had died of septicaemia, who had received corticosteroids, and that was I think the basis for his opposition. It's right that if you have seen someone have a haemorrhagic stroke after you have given streptokinase, it makes it far more difficult to say that this is a policy that we should adopt, because you actually don't know which of your patients would have died if you hadn't have given it to them. But in fact it wasn't the case in St Davids. In St Davids they had adopted steroids on the basis of the trials. This study that Roger did was a retrospective assessment which didn't, they didn't take it up, they had taken it up to a greater extent than University Hospital of Wales, and that was as you said in fact based on the Liggins and Howie trial.

Hayward: I wonder whether it might be useful briefly describing intervention that I led on over a two-year period, which was partly triggered by Richard's list of suggested effective interventions that should be used for perspective audit by obstetricians under the banner of the RCOG. I will need about four minutes to describe it. I am Director of Public Health in Newham, but I am really here because I was then a public health specialist in training at Camden and Islington health authority, and I have known Iain for years, because I am married to his sister. It took me 10 years to really get a grip on what he had been going on about, about evidence. But there's nothing like a convert late in life to become a passionate advocate, so having at last seen the light after 10 years it made me very interested to know quite why other people were having equivalent problems.

Professor John Gabbay, born 1949, qualified in medicine at Manchester in 1974. After 7 years at the University of Cambridge working on the social origins of medical knowledge, he trained in public health and in the 1980s carried out qualitative research on NHS management and clinical audit. From 1992 to 2004, when he retired, he directed the Wessex Institute of Health R&D, which now houses the National Coordinating Centre for Health Technology Assessment, which he also directed. His recent research has focused on the implementation of evidence in clinical practice.

THE WELLCOME TRUST

WITNESS SEMINARS

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Witness seminars are intended to address issues of medical–historical interest in the latter half of the twentieth century. The entire proceedings are recorded and transcribed by the Wellcome Trust with a view to publication to generate interest in, and provide material sources for, the study of significant events in recent medical history. As copyright in anything you said during the proceedings belongs to you (copyright in the recording of the proceedings belonging to the Wellcome Trust), we would be grateful if you would complete this form to enable the Wellcome Trust to use your contribution in the manner and for the purposes outlined above.

****

1. NAME **Professor John Gabbay FFPHM RCP**

2. ADDRESS
University of Southampton, School of Medicine, Department of Biomedical Sciences Boldrewood, Bassett Crescent East Southampton SO16 7PX

3. WITNESS SEMINAR: **Prenatal Corticosteroids for Reducing Morbidity and Mortality**
15 June 2004

4. ASSIGNMENT

I confirm that I am the author and legal owner of my contribution to the proceedings of the Witness Seminar and of any comments I may have made on any draft transcript ("my Contribution"), and I assign to the Trustee of the Wellcome Trust ("the Trust") the copyright in my Contribution.

5. SOUND RECORDING

I confirm that the entire copyright and all other rights in the sound recording made of my Contribution by the Trust at the Witness Seminar ("the Sound Recording") and the transcript made of the Sound Recording belong to the Trust for the full period of copyright including all renewals and extensions.

6. PUBLICATION

I acknowledge the right of the Trust as assignee of the copyright in my Contribution to publish my Contribution in whole or in part.

I acknowledge the right of the editor of any publication of my Contribution to edit my Contribution provided that my approval of any changes made by the editor will be obtained (such approval not to be unreasonably withheld).

7. USE OF MY CONTRIBUTION

I reserve the right to make use of my Contribution, having first obtained the permission of the Trust for me to do so (such permission not to be unreasonably withheld) and I confirm that in any such use I will acknowledge the Trust.

Signed..... Date..10/1/05

Lois Reynolds

From: Gabbay J. [J.Gabbay@soton.ac.uk]
Sent: 01 June 2005 11:54
To: ucgarey@ucl.ac.uk
Subject: RE: Witness Seminar: Corticosteroids, 15 June 2004

Oh dear - that's worrying. I posted them without keeping a copy, and I certainly can't recall what they were except that they were few but - I thought at the time - quite important corrections/ clarifications. .
Could you send me another copy or fax me the pages where I "appear"?
You'll need to warn me to switch the fax on if the latter.
My fax is the "usual telephone" number below)
Jx

John Gabbay
Emeritus Professor, University of Southampton.
1 Daniells Close
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Usual telephone: +44 (0) 1590 671918
Office telephone: +44 (0) 2380 595649
Mobile: +44 (0) 7774 890016

Email: j.gabbay@soton.ac.uk <mailto:jg3@soton.ac.uk>

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-----Original Message-----
From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: 01 June 2005 11:28
To: J.Gabbay@soton.ac.uk
Subject: Witness Seminar: Corticosteroids, 15 June 2004

Dear Professor Gabbay,

I've taken over the editing of this transcript from Daphne Christie and notice that no corrections have been received since your email of 10 January 2005 with your biographical note.

I would be grateful for any changes that you wish to have included in the text.

Best wishes from Lois Reynolds

Mrs Lois Reynolds

Research Assistant to Dr Tilli Tansey
History of Twentieth Century Medicine Group
Wellcome Trust Centre for the History of Medicine
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210 Euston Road,
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email: l.reynolds@ucl.ac.uk
Fax: 020 7679 8192
www.ucl.ac.uk/histmed/witnesses.html

The Wellcome Trust Centre is supported by the Wellcome Trust, a registered charity, no. 210183.

Gabbay

see pages 22, 23, 77-8, 79
and biographical note: 113

All OK
No changes
needed.

PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY IN PRETERM BIRTH

The transcript of a Witness Seminar held by the Wellcome Trust Centre for the History of Medicine at UCL, London, on 15 June 2004

Edited by L A Reynolds and E M Tansey

11/8/05

-3 10.3.05; -4 7.07.05; -5 28.7.05;-6 4.8.05 (2nd); printed: 5 August 2005

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rec'd 2/9/05 ✓ aeK 5/9/05
for return by 7 Sept 2005

Prenatal Corticosteroids for Reducing Morbidity and Mortality In Preterm Birth

Participants

Dr Mary Ellen (Mel) Avery
Sir Christopher Booth
Dr Peter Brocklehurst
Sir Iain Chalmers
Dr Patricia Crowley
Professor John Gabbay
Professor Harold Gamsu†
Dr Dino Giussani
Mrs Gill Gyte
Dr Stephen Hanney
Professor Jane Harding
Dr John Hayward
Dr Edmund Hey (Chair)
Dr Ian Jones
Professor Richard Lilford
Professor Miranda Mugford
Mrs Brenda Mullinger
Professor Ann Oakley
Dr Sam Richmond
Dr Roger Vernier Jones
Professor Dafydd Walters
Mr John Williams

Among those attending the meeting:

Professor Richard Beard, Dr Sheila Duncan, Professor Abby Fowden, Dr Anita Magowska, Dr John Muir Gray, Professor Alison Macfarlane, Dr David Paintin, Professor Maureen Young

Apologies include:

Professor Sir Robert Boyd, Dr Clive Dash, Professor Geoffrey Chamberlain, Dr Pamela Davies, Professor Sir Liam Donaldson, Professor Peter Dunn, Dr Jonathan Grant, Professor Aidan Halligan, Professor Mark Hanson, Professor Ross Howie, Professor Frank Hytten, Professor Marc Keirse, Professor Sir Graham Liggins, Dr Jerold Lucey, Professor Sally MacIntyre, Dr Jonathan Mant, Professor Jim Neilson, Dr Cliff Roberton, Ms Barbara Stocking, Dr Peter Stutchfield, Dr Peter Williams, Professor Mark Walport, Professor Jonathan Wigglesworth

†Died 31 August 2004

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19th March 2004

Dear Professor Gamsu

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004
2.00 pm – 6.00 pm

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is organising a Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15th June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1 2BE. Dr Edmund Hey has kindly agreed to chair the meeting and Sir Iain Chalmers is assisting us in the organisation.

Sir Iain Chalmers has recommended that we invite you to this meeting and we would be delighted to have you join us.

As you know, these seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history. I enclose a flyer of our recent publications to illustrate the range of topics we cover.

Continued/... Page 2

We are in the process of inviting senior scientists, clinicians, and representatives from relevant organisations to attend the meeting and hope to promote a lively discussion.

We will be providing further details in due course and would particularly appreciate, at this stage, suggestions of possible participants.

I look forward to hearing from you and do hope you will be able to accept this invitation.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

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26 April 2004

Dear Professor Gamsu

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004, 2pm–6pm

We are delighted that you are able to attend the above meeting and are happy to tell you that plans are proceeding well. A copy of our publicity material is enclosed and I will be sending you a draft programme in due course. A full attendance list will be available at the meeting.

We will be asking some participants to "start the ball rolling" by saying a few words on specific subjects, as we like to prime a few people to lead off the discussions, although there will be ample opportunity to contribute throughout the meeting. We do not show slides or overheads at the meetings, as we wish to encourage informal interchange and conversation. If however, you would like any material to be available to the audience, we could photocopy a diagram or article for you, and leave a copy on every chair.

Please do not hesitate to contact either myself or Mrs Wendy Kutner 020 7679 8106 if you have any queries prior to the meeting.

We very much look forward to seeing you at the meeting.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

enc.

The Wellcome Trust Centre for the History of Medicine at University College London is funded by the Wellcome Trust, which is a registered charity, no. 210183. Histmed logo images courtesy *Wellcome Library*, London.

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16 June 2004

Dear Professor Gamsu

The Wellcome Trust History of Twentieth Century Medicine Group Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with pretern birth

May I say on behalf of The History of Twentieth Century Medicine Group and the co-organiser, how grateful we are to you for your contributions to yesterday's meeting? It really was a splendid occasion, and we hope that you enjoyed it as much as those of us who were observers.

As mentioned in previous correspondence and at the meeting, the taped proceedings of the meeting will now be sent for transcription, and we hope to have a draft manuscript to send you in about six months time for your comments. Ultimately we intend to publish an edited version of the proceedings, and you will be sent a copyright assignment form and final proof before publication.

Yours sincerely

Daphne Christie

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

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5 January 2005

Dear Mrs Gamsu

Witness Seminar: Prenatal Corticosteroids for reducing Morbidity and Mortality 15 June 2004

I was so sorry to hear about the passing away of your husband and trust that it is acceptable for me to contact you at this time.

I have enclosed a draft transcript of the Witness Seminar on '**Prenatal Corticosteroids for reducing Morbidity and Mortality**' to which your husband contributed. We intend to publish a version of the transcript in November 2005 under the auspices of the Wellcome Trust Centre for the History of Medicine at UCL.

I would be most grateful if you could check your husband's contributions for general sense, accuracy and typographical mistakes. We do not encourage extensive alterations, as the purpose of these publications is to retain the freshness and informality of the meeting. However, any additional information can be added as a footnote and you may like to suggest such material Please mark all corrections clearly on this copy and return it to me by **Friday 4 February.** Earlier published volumes in the series can be viewed on our website, www.ucl.ac.uk/histmed/witnesses.html

- Please sign and return the standard form assigning copyright to the Wellcome Trust.
- We would like to include illustrations of early work in the volume. If you have any suitable images or figures, please include these with the pages. They will be carefully scanned and returned in protective packaging.
- A final proof version, incorporating the changes made by all the participants, added footnotes, and any queries will be sent to you in **September 2005** for return within a week**. At this stage only minor corrections, such as those of a typographical nature, will be possible**.

The tapes, earlier versions of the transcript, and any additional correspondence generated by the editorial process, will be deposited in the Wellcome Library.

A version of the transcript will also be mounted on the Wellcome Trust Centre's website shortly after publication.

Thank you for your help at this difficult time.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

THE WELLCOME TRUST

WITNESS SEMINARS

COPYRIGHT ASSIGNMENT

Witness seminars are intended to address issues of medical–historical interest in the latter half of the twentieth century. The entire proceedings are recorded and transcribed by the Wellcome Trust with a view to publication to generate interest in, and provide material sources for, the study of significant events in recent medical history. As copyright in anything you said during the proceedings belongs to you (copyright in the recording of the proceedings belonging to the Wellcome Trust), we would be grateful if you would complete this form to enable the Wellcome Trust to use your contribution in the manner and for the purposes outlined above.

****

1. NAME Mrs Harold Gamsu for Professor Harold Gamsu

2. ADDRESS 26 Calton Avenue, Dulwich, LONDON SE21 7DE

3. WITNESS SEMINAR: Prenatal Corticosteroids for Reducing Morbidity and Mortality
15 June 2004

4. ASSIGNMENT

I confirm that I am the author and legal owner of my contribution to the proceedings of the Witness Seminar and of any comments I may have made on any draft transcript ("my Contribution"), and I assign to the Trustee of the Wellcome Trust ("the Trust") the copyright in my Contribution.

5. SOUND RECORDING

I confirm that the entire copyright and all other rights in the sound recording made of my Contribution by the Trust at the Witness Seminar ("the Sound Recording") and the transcript made of the Sound Recording belong to the Trust for the full period of copyright including all renewals and extensions.

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I acknowledge the right of the editor of any publication of my Contribution to edit my Contribution provided that my approval of any changes made by the editor will be obtained (such approval not to be unreasonably withheld).

7. USE OF MY CONTRIBUTION

I reserve the right to make use of my Contribution, having first obtained the permission of the Trust for me to do so (such permission not to be unreasonably withheld) and I confirm that in any such use I will acknowledge the Trust.

Signed..... Date 22.1.05

Gamsu

~~Hardiff~~
~~Corticois~~

see pages 54-6, 63, 84-5, 100
biographical note: 114

PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY IN PRETERM BIRTH

The transcript of a Witness Seminar held by the Wellcome Trust Centre for the History of Medicine at UCL, London, on 15 June 2004

Edited by L A Reynolds and E M Tansey

11.8.05

-3 10.3.05; -4 7.07.05; -5 28.7.05;-6 4.8.05 (2nd); printed: 5 August 2005

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spare pages removed 27/9/05
corrected 27/9/05.

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Prenatal Corticosteroids for Reducing Morbidity and Mortality In Preterm Birth

Participants

Dr Mary Ellen (Mel) Avery
Sir Christopher Booth
Dr Peter Brocklehurst
Sir Iain Chalmers
Dr Patricia Crowley
Professor John Gabbay
Professor Harold Gamsu[1]
Dr Dino Giussani
Mrs Gill Gyte
Dr Stephen Hanney
Professor Jane Harding
Dr John Hayward
Dr Edmund Hey (Chair)
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Among those attending the meeting:

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[1]Died 31 August 2004

trial completed and published more than five years ago, that they can still find the original raw paperwork? One of the most amazing things that I found in reading around before today's meeting, was to come across this paper by a Jane Harding in the *American Journal of Obstetrics and Gynecology* on just this subject, published in 2001, and this is control trial data, and it has sat there all that time.[82]

Harding: Yes. I think there are a number of messages. One is the data was still there and still in a form that we could use, which I think is very impressive. The second is that new questions have come up that the trials weren't necessarily designed to answer at the time, but it's terribly important that the data is still there.[83] Thirdly, someone might like to comment on the length of time it took us to get that paper published. The study was done in 1996–97, we wrote it up in 1998, it was rejected by two journals, submitted to the *American Journal of Obstetrics and Gynecology* in 1999, and it was eventually published in 2001. I do think the people who publish have something to contribute to this very prolonged process.

If I could just go onto the other issue that was raised, what about the women who get steroids and don't deliver? We have been concerned about this with respect to the repeat steroid issue. There has been a multi-centre randomized trial being run by Caroline Crowther out of Adelaide for the last seven years.[84] We hope to finish recruiting this month. It includes 980 women, and we have been doing huge detailed studies of the babies in Auckland, the second largest centre recruiting to this trial. It occurred to us early on in that trial that we still

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[82] Harding *et al.* (2001).

[83] See Peter Elwood's description of planning the Caerphilly study in Reynolds and Tansey (eds) (2005): 81.

[84] See also Crowther C A, Harding J. (2003) Repeat doses of prenatal corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2003. Chichester: John Wiley & Sons, Ltd.

didn't have good data about risks and benefits for that group [?:which??], the group who don't stand to achieve the greatest benefit for the infant and are potentially at the greatest risk. Once again we thought the data wasn't out there but I bet it was in the original trial. Once again we were able to go back to the original data, look specifically at that group, write a new meta-analysis which has also been published after many rejections, after a very long time, which showed, in fact, that there may be adverse effects in that group.[85] Therefore people need to randomize them to the new trials. We were in fact trying to help recruitment of the randomized trials. It took so long to publish that. I think it's had very little effect on recruitment to the trial, but the data are nevertheless there. Yet another outcome that was not relevant at the time, the question has come up subsequently.

Hey: Would Glaxo still be able to find the data?

Professor Harold Gamsu: Oh yes, I have all the data in my office.[86] It's still there, all the data sheets, because I was hoping to do a long-term follow up on

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[85] McLaughlin *et al.* (2003).

[86] Gamsu *et al.* (1989). See? Protocol and case record, in Figure ??? Dr Clive Dash wrote: 'The retention of clinical trial data in the 1970s–80s was poor. This has changed in recent years. When Harold Gamsu persuaded us to do a detailed analysis of the UK study, the computer software had changed and so had most personnel acquainted with the prior system. Luckily, Alex Paton at Glaxo was able to interrogate the database and through her efforts we were able to meet Harold's expectations and answer his critical questions. Also, Harold volunteered to keep safe the original case record forms and other study documentation when Brenda Mullinger and I left Glaxo to pursue other career opportunities. I believe Harold always hoped to trace the babies in adult life to address the question of the long-term safety. It is due to his diligence and enthusiasm that he persuaded us (again, pleasantly) in 2001 to begin the process towards a 30+ years follow-up. His untimely death occurred in August 2004, soon after this Witness Meeting. We hope to continue this project with the support of NPEU in Oxford provided external support can be mobilized and plan to dedicate any outcomes to his memory.' E-mail to Dr Daphne Christie, 10 January 2005.

the adults, and in fact things haven't turned out that way, but that's still available for people to do if they would like to.

Hey: Because people are still asking the questions: 'Does it work in twins?' or 'Should you give it in mothers with hypertension?'

Gamsu: Our numbers, of course, are very small.

Hey: So are everybody's, but if people have kept their data, there are more that can be analysed that has not yet been done. Could anybody find the NIH data? Would the NIH people share their data?

Avery: I have no idea.

Gamsu: May I ask a question about this study by Newnham and Co? My feeling is that it is animals, but could you tell us a little bit more, because it sounds very significant if it's not animals.

Brocklehurst: I cannot tell you very much more, because I heard it presented in Glasgow about six weeks ago, but I have seen nothing in the press yet.[87] My recollection is that it was in animals, but we'll be able to explore this further

[87] Professor John Newnham from the King Edward Memorial Hospital, University of Western Australia, Perth, Australia, delivered the Society Lecture, 'Antenatal Steroids and Outcome', at the British Maternal and Fetal Medicine Society's Ninth Annual Conference, 1–2 April 2004, held at the Scottish Exhibition and Conference Centre (SECC), Glasgow. He presented results from human and animal studies where infants had been exposed to steroids before birth. See the full report by Dr Margaret M Ramsay, Honorary Secretary, BMFMS at www.bmfms.org.uk/presssummaryofglagow04.doc (visited 18 July 2005).

when the study is published.[88] Having tried to do one of the large trials of multiple courses of steroids, I think one of the issues with clinicians about the use of multiple courses of steroids is that their threshold for starting antenatal steroids is lower, because if they are wrong, and the woman doesn't deliver soon, they have felt that they can always give a second course. If people are restricted to giving a single course of steroids they may delay starting until there is stronger evidence, if you like, of impending preterm birth. So the groups of women selected into these trials is likely to be quite different from the multiple steroids group and that will make the interpretation of the results interesting.

Lilford: I recently had a debate with my 14-year-old daughter Philippa about whether history is just an interesting thing to read, or whether it helps us to design our own futures. Listening to Jane speak makes me think that there really are occasions when history has a lesson for the future. Hearing you speak about finding these records has been very interesting, but I suspect that many people in this room were amazed that you really could find those source materials after 30 years, that you could find the trial documents and so on. When Harold Gamsu moves the documents from his office, goodness knows where they might go. So the lesson that we might want to learn from this is the importance of some sort of systematic paid for-archive for trial information and I don't know if you might want to comment. I know that the Economic and Social Research Council (ESRC) archive their most precious data and build the cost of so doing into the grant.[89] The more I hear the more I think this might be something we ought to try to take forward as a matter of some urgency.

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[88] The lecture will be published in 2006 as: Newnham J P. (in press) The steroid story: iconic advance or ticking bomb? *Yearbook of Obstetrics and Gynaecology*, vol. 12. London: The College.

[89] The Economic and Social Data Service (ESDS) Qualidata is a specialist service of the ESDS led by the UK Data Archive (UKDA) at the University of Essex. The service provides access and support for a range of social science qualitative datasets. Established in 1967 the UKDA holds the largest collection of digital data in the social sciences and humanities in the UK, funded by the ESRC,

Gamsu: I agree with you. The cost of anything is almost always invested in the cost of salaries, particularly nurses, of course, because they have to be there all the time.

Hey: And at night as well. They are now expected to have only one baby in their care.

Mugford: We can say that over the last 20 years the resources devoted to neonatal intensive care, you had a different seminar on this subject[96] – I haven't looked at the living witness results on [??transcript of??] that seminar – but [?what has expanded?]having incredibly expanded and there are very many more nurses, doctors, ventilators and techniques for the care of preterm babies than there were 20 years ago.[97]

Hey: I think we shall move straight on, because we examine next how to get research into practice. I am going to ask Iain to explain how it came about that he chose to use a very early version of Patricia's meta-analysis as late as 1992, at a time when there were twice as many trials involved in her analysis for his Cochrane Center logo.

Chalmers: It's good that Patricia Crowley has already described some of the history. Given that I am going to be talking about the Cochrane logo, I might as well start with Archie Cochrane, whose famous book – *Effectiveness and Efficiency: Random reflections on health services* – was published in 1972.[98] I read

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[96] See the Witness Seminar, 'Origins of Neonatal Intensive Care in the UK', Christie and Tansey (eds) (2001), also freely available online at www.ucl.ac.uk/histmed following the link to Publications.

[97] Macfarlane A, Johnson A, Mugford M. (1999) Epidemiology, in Roberton N R C, Rennies J. (eds) *Text book of Neonatology*, 3rd edn. Edinburgh: Churchill Livingstone, 3–33.

[98] Cochrane (1972).

it in 1973 and it changed my life![99] In spite of the fact that I had been 'licensed to kill' six years earlier after studying at the Middlesex Hospital Medical School, London, to qualify as a doctor, I had not previously been aware of the term 'randomized controlled trial (RCT)'. Cochrane showed me how I might adjudicate among incompatible clinical opinions about treatments, a common situation faced by me and other junior doctors, and it was after reading Cochrane's book that I started to collect reports of RCTs. A librarian in Cardiff, Steve Pritchard, designed a Medline search to identify these studies for me, and I started noting those in my special area of interest (perinatal care) during my reading of journals and books.

In 1976, because it was clear that this was an insufficiently systematic method of finding reports of RCTs, I outlined a plan for using a more systematic approach both for finding published reports, and for identifying unpublished studies (because biased under-reporting of RCTs means that unpublished studies tend to have less dramatic results than those that get into print). This plan, which was set out in a letter to Martin Richards, a psychologist in Cambridge, also stated an intention to use statistical synthesis of the results of similar by separate studies (meta-analysis) to reduce Type 2 errors (false negatives) in estimating treatment effects. My letter to Martin Richards happened to be sent to him during the same year as the term 'meta-analysis' was introduced by the American social scientist Gene Glass.[100]

The first opportunity that I took to do a systematic review using meta-analysis related to different ways of monitoring babies during labour.[101] Electronic fetal heart rate monitoring had been introduced in obstetrics not long previously, sometimes accompanied by fetal scalp blood sampling to assess fetal acid-base status, particularly if the heart rate trace had raised concerns. It was being suggested by some people that these more intensive methods of intrapartum

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[99] Chalmers (1999).

[100] Glass (1976).

[101] Chalmers (1979).

Apart from power, I think that vested interests, empire building and struggles and political competition between trusts were barriers – this was the time of the purchaser–provider split and market competition was a really important issue around 1995/6. The main barrier was fear of something going horrendously wrong. People would then distort their perception of the evidence and vigorously resist on being told to do something that they didn't think was safe to do, regardless of the evidence. After about six months the staff went through a series of educational events at this particular hospital and eventually decided to start to introduce ECV and as far as I know it is now common policy. But we couldn't make them do it, they had to decide to do it themselves, and they had to take their clinicians with them. I think it was a painful and difficult process for them everyone.

May I just mention the main conclusions from this particular piece of work? Don't expect this sort of study to get it into the *British Medical Journal.* It won't be accepted. Secondly, advocates are really important when it comes to getting guidelines adopted and I think opinion leaders are really important within institutions, but the important thing is that the guidelines have got to be written in such a way to be usable, understandable and accessible to those who are going to implement them. That means clear inclusion and exclusion criteria. Another important agent for change are the users, and if you have women asking these sorts of questions, after a while people do get a bit embarrassed coming up with the same answers that clearly won't be supported by evidence or by colleagues. I would like to see women users being far more involved in ways in which we can encourage the implementation of best practice. I am not surprised that there was no sign of managers actually implementing any change in Richard's study. It's a scary business. There was blood all over the carpet when we were dealing with the ECV meetings, and it required somebody – like the users who were tough, or somebody like me who's a public health specialist and who has been a GP and is not afraid of consultants – to hold the line if necessary. Managers cannot do that, and I don't think we should expect them to. I think it's exceedingly difficult. The

most important barrier, the most important influence to achieve change, is the personal experience of the person making the clinical decision. When new interventions are being rolled out we must encourage people to be at the centre of it, so they get feedback of the positive results. Then it is much easier to get change implemented.

Hey: That rings true for a lot of us, I think. You went over time, but I think you said something very important. We are beginning to get very tight for time and so I am going to ask Stephen Hanney to speak next. But Harold [Gamsu], while you were out of the room we did hear that quite a lot of units said that they couldn't join your trial, because they were already using it so widely and that occurred at the time when in actual fact we know that ess than 6 per cent were really using steroids nationally l. Did being involved in the trials themselves influence the centres? Did the centres that had been involved in the research take up the outcome of that research more than those who only read about it?

Gamsu: I don't know the answer to that I am afraid. We didn't follow that point up, but as far as I know Brenda Mullinger might know something about it. All I can say is that there were local reasons that indicated against the use of steroids. There was quite a lot of gossip about this and we have heard some examples of this today. The risk of infection especially in ruptured membranes, and the unexplained deaths in hypertensive women from Liggins's original report which turned out to be spurious.

The other thing that I found was influencing obstetricians was the increased risk of pulmonary oedema which people widely accepted as a complication of steroid therapy. In fact it was a complication of tocolytic agents that were used, especially when those agents were given in large volumes of fluid. As far as I know, steroids given alone were not tocolytic agents and did not result in pulmonary oedema. So I think we had quite a lot of persuading to do even in

those places that accepted that they would be in the trial. I know that Brenda Mullinger and Clive Dash from Glaxo had a lot of difficulty keeping the momentum up, trying to recruit women, even though ..... [?] were reaching the volunteers. As you possibly remember from the paper, 60 per cent of the cases came from patients who were recruited from three hospitals, the rest of them just put it away.

Hanney: We at Brunel have been looking at the benefits from health research for about ten years now, and this particular stream of work seems to us to have been one of the most interesting, and [that] I have worked on ~~it~~ with Miranda, Martin Buxton and Jonathan Grant. I apologize for checking my notes from time to time, because I am trying to pick up what various people have said today in what I think is an interesting session.

For instance, John [Hayward], we at least read your work. There is a paper that sets out most of this in detail in press and will be published in *Social Science and Medicine*.[147] I will just highlight all the key points for now. Perhaps it's just worth spending a minute, going over our payback framework so you can see how we tried to drop this stream of work into a frame [?model?] that we had already developed. Apologies to those who have already heard this many times before. Basically, there are two aspects to our payback framework: a multidimensional categorization of benefits, and a model to examine how they arrive. The categories which we suggest are five: knowledge production; the targeting of future research and building research capacity; better informing policies, with the term policies being widely interpreted; health gain and benefits to the health sector; and the broad economic benefits. There's a series of stages in the model in which we think these various benefits can be identified. A key feature of our model is to attempt to identify actual levels of uptake so that we can then say what the benefit has been, and this, of course, links with previous discussions.

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[147] Hanney *et al.* (2005).

perfectly reasonable justification for raising the age at which you can vote.[174] But babies develop, they develop for a long, long time and something like steroids has an enormously potent effect on all the systems of the body, and yet we think we can just look at RDS and ignore the potential long-term effects. I think we are beginning to realize that we cannot do that, that interventions which show short-term benefits, like neonatal dexamethasone, may be countered by long-term harm. Not that there is no benefit in the long term, but that the long-term effects may be in the opposite direction. This means that long-term follow up studies of these trial cohorts become essential and yet the current situation [?of funding??] in the UK, I would suggest, is making it more and more difficult and more and more expensive in terms of being able to follow-up people.

Hey: I would just add one thing that you didn't raise. One of the issues about which steroids may have adverse effects is that some of the steroids have sulphides added to them as a preservative, but nobody reads the label, they think betamethasone *is* betamethasone. You can get betamethasone with a sulphide preservative in it and that was what was used in the recent French observational study. Liggins managed to choose the very best steroid in the very best dose that required just two injections. The preparation he used was also preservative-free.

Brocklehurst: I think there is an issue here about preparations, because I remember [??who??, from??] the Canadian study got in touch with us about our TEAMS trial, and asked, 'How [?Where?] did you get a placebo for your betamethasone, because ours is cloudy?' We replied that ours was completely clear. The original trial doesn't specify what the betamethasone preparation was and we were using the betamethasone that was available in this country, and in the UK you can only buy betamethasone in a solution, not a suspension.

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[174] Wallis (2004).

Gamsu: This is why, of course, with the advice of Glaxo we chose the three-dose regimen of betamethasone phosphate to try to achieve the same sort of levels as the 12-hourly regime that was used in New Zealand and also the placebo that was used was the vehicle and has the same appearance as the steroid that was used. And of course there's a slight caveat about the use of cortisone acetate as the placebo in the Liggins trial, in which way it influenced things, if it did at all, one cannot say.

Hey: Perhaps we had better clarify that. They used, rather than having a negative placebo in the original Liggins trial, a corticosteroid which was only one seventieth as powerful, because it didn't cross the placenta.

Gamsu: It did cross but in much smaller quantities.

Hey: But by choosing that, they had something that looked visually identical. So one of the good things about the original trial was that they were genuinely blinded and I keep on hearing stories about how the second biggest trial, the US NIH Collaborative Group trial, is seriously flawed because there were unblinding issues.

Harding: If I could just comment on that? Mont did actually check the effects of the cortisone acetate, the placebo, on the babies, and in, I don't know how many, women, but he measured cord blood steroid levels and showed that twice the dose used as placebo had no effect on cord blood steroid levels and that reassured him that that was an appropriate placebo.

To come back to Peter Brocklehurst's point about how come they chose the best dose and the best drug, I don't think we know that they did. Nobody's looked and almost all of the issues that Peter has raised – the repeat steroids, which dose, which drug, how often, at what gestation, to which pregnancy – all

Sir Iain Chalmers

FRCPE FFPH FMedSci (b. 1943) has been Editor of the award-winning James Lind Library since 2003. He was Director of the UK Cochrane Centre in Oxford from 1992 to 2002 and Director of the National Perinatal Epidemiology Unit, Oxford, from 1978 to 1992. See www.jameslindlibrary.org/ (visited 2 June 2005).

Professor Archie Cochrane

CBE MBE FRCP FFCM (1909–88), medical scientist and epidemiologist, whose first clinical trial was conducted as a prisoner of war in Salonika. Following the war he was appointed to the Medical Research Council's Pneumoconiosis Research Unit in 1948. In 1960 he was appointed David Davies Professor of Tuberculosis and Diseases of the Chest at the Welsh National School of Medicine, Cardiff, becoming Director of the Epidemiology Research Unit there in 1961 until his retirement in 1974. His papers are available for study at the Cochrane Archive, Llandough Hospital, Penarth, Cardiff. See Cochrane (1976); Cochrane [ALC] (1988). See also Ness *et al.* (2002).

Dr Patricia Crowley

FRCOG FRCPI (b 1951) has been a consultant Obstetrician Gynaecologist at the Coombe Women's Hospital, Dublin, and Senior Lecturer at the Department of Obstetrics and Gynaecology, Trinity College Dublin since 19xx.

Dr Clive Dash

FFPM (b. 1940) graduated from University of Birmingham and did post-graduate obstetrics with Professor Hugh McLaren in Birmingham, and has spent most of his professional life in clinical research within the pharmaceutical industry. He instigated and coordinated the UK trial of antenatal steroids in 1974 while working as a clinical research physician for Glaxo in the UK. He has been an independent consultant in healthcare and pharmaceutical medicine since xxxx, while continuing his clinical practice in thoracic medicine.

Professor Geoffrey Dawes

CBE FRCOG FRCP HonFACOG FRS (1918–96), qualified at Oxford in 1943, spent a year? at Harvard in 1946. He was Director of the Nuffield Institute for Medical Research, Oxford, from 1948 to 1985., as well as a Governor of Repton, 1959–88, and Vice President of the Royal Society, 1976–77. See Liggins G (1998). Geoffrey Sharman Dawes, *Biographical Memoirs of Fellows of the Royal Society* 44: 110–25.

Professor John Gabbay

FFPHM (b. 1949) qualified in medicine at Manchester in 1974. After working on the social origins of medical knowledge for seven years at the University of Cambridge, he trained in public health and carried out qualitative research on NHS management and clinical audit in the 1980s. From 1992 until his retirement in 2004 he was Professor of Public Health and Director of the Wessex Institute of Health Research and Developmentat the University of Southampton, which houses the National Coordinating Centre for Health Technology Assessment, of which

he was former director. His recent research has focused on the implementation of evidence in clinical practice.

Professor Harold Gamsu

FRCP FRCPCH (1931–2004) graduated in Johannesburg in 1954. His training in paediatrics commenced there, and continued at the University of Sheffield and ~~xx~~ in Cleveland, Ohio. He was appointed as Wates Fellow at King's College Hospital, London, in 1965, ~~then~~ Senior Lecturer, Reader in Paediatrics and Director of the Neonatal Unit, 1979, and in 1994 Professor of Neonatology until his retirement in ~~xxxx~~, later Emeritus. He established the London Perinatal Group in the 1970s, later known as the Thames Regional Perinatal Group.

Dr Dino Giussani

PhD (b. 1967) received his PhD in Fetal Medicine at UCL and has conducted post-doctoral work at the University of Chile and Cornell University. He was appointed university lecturer at the University of Cambridge in 1993; has been Fellow of the Lister Institute for Preventive Medicine there, since 2001 and a Reader in Developmental Cardiovascular Physiology and Medicine since 200x, and Director for Studies in Pre-clinical Medicine at Gonville and Caius College, Cambridge, since 200x.

Mrs Gill Gyte

MPhil (b. 1948) has been an antenatal teacher with the National Childbirth Trust (NCT) since 1985. She was a volunteer worker on the NCT Research and Information Group from 1990 to 1997 and has been the Consumer Panel Coordinator for the Cochrane Pregnancy and Childbirth Group since 1997.

Dr Stephen Hanney

PhD (b. 1951), trained as a political scientist, has specialized in examining evaluation and policy making in higher education and research. Since 1993 he has worked with [Professor] Martin Buxton at the Health Economics Research Group, Brunel University, London, developing and applying techniques of assessing payback or benefit from health research.

Professor Jane Harding

ONZM DPhil FRACP FRSNZ (b. 1955) obtained her medical degree at the University of Auckland in 1978 and completed a DPhil in fetal physiology at the University of Oxford in 1982. After specialist paediatric training in New Zealand and a postdoctoral fellowship at the University of California at San Francisco, she joined the faculty of xx at the University of Auckland in 1989 and was appointed Professor of Neonatology in 1997. She works as a specialist neonatologist at National Women's Hospital. She also heads the fetal physiology laboratory and is Deputy Director of the Liggins Institute at the University of Auckland.

Dr John Hayward

FFPH(b. 1946) was in general practice for 16 years before re-training in public health. From 1994/6 he led the Effective Care Project in maternity services for the Camden and Islington Health Authority.

Harold Gamsu

1/21a/05

A pioneer in the development of neonatal intensive care

GAMSU
died 31 Aug 04

Harold Gamsu, professor of neonatology King's College Hospital, London, 1965-93 (b W[illegible] Witwatersrand, South Africa, 19[illegible]31 August 2004 from complications [illegible]

Harold Gamsu was born in Windh[illegible] Russian Jewish émigrés, and was th[illegible] university. After qualifying he work[illegible]ican State Hospital in Windhoek. He began his [illegible]ining in paediatrics with Professor R S Illingworth at Sheffield Children's Hospital and then moved with his wife and four young children to Ohio, United States, to work with Dr F Robbins and Dr R Schwarz at the Cleveland Metropolitan General Hospital. He then returned to work in Namibia before taking up a post in paediatrics at King's College Hospital, London, subsequently becoming professor of neonatology.

Harold was a pioneer in the development of neonatal intensive care in the United Kingdom. In the course of the 30 years that he spent at King's College Hospital, the neonatal unit became a nationally recognised centre of excellence. His contribution to the development of neonatal services and care in the region, and nationally, was considerable.

Harold was a founding member of the South East Thames Regional Perinatal Monitoring Group (RPMG) and its first chair. The RPMG provided multidisciplinary advice on maternity and neonatal care to the regional director of public health from 1977 to 1996. He established that there was a need for regional neonatal services and was instrumental in developing centres of excellence outside London. Hospital visits and an appraisal process ensured that quality of care was being maintained. The RPMG, in which Harold was prominent, guided developments and improvements in maternity and neonatal services for the region and sought to achieve consensus for major projects, such as the introduction of the first computer system for neonatal and maternal care. One of Harold's strengths was that he tenaciously pursued projects from development through to implementation.

He also drove forward and chaired the South East Thames Confidential Review into Perinatal Deaths from 1987 to the advent of the national Confidential Enquiry into Stillbirths and Deaths in Infancy in 1992. Harold was instrumental in securing a regional study into the causes, management, and outcome of very low birthweight babies, which has accumulated many years of data, and he also initiated a national survey on necrotising enterocolitis. During his period of involvement with the British Association for Perinatal Medicine he was seen by colleagues as very determined, immensely hard working, and wise; "a gentle giant of a man."

As a clinician, he had exceptional skills and set himself very high standards; his core ethos was a

1/21/05

Harold Gamsu

A pioneer in the development of neonatal intensive care

Harold Gamsu, professor of neonatology King's College Hospital, London, 1965-93 (b Windhoek, Namibia, 1931; q Witwatersrand, South Africa, 1954; FRCP Ed, FRCP), died on 31 August 2004 from complications following abdominal surgery.

Harold Gamsu was born in Windhoek, Namibia, the son of Russian Jewish émigrés, and was the first of his family to go to university. After qualifying he worked at the African State Hospital in Windhoek. He began his training in paediatrics with Professor R S Illingworth at Sheffield Children's Hospital and then moved with his wife and four young children to Ohio, United States, to work with Dr F Robbins and Dr R Schwarz at the Cleveland Metropolitan General Hospital. He then returned to work in Namibia before taking up a post in paediatrics at King's College Hospital, London, subsequently becoming professor of neonatology.

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As a clinician, he had exceptional skills and set himself very high standards; his core ethos was a

holistic approach—considering the needs of the whole family. A testimony to his passionate and devoted care were the many messages of condolence and the presence of parents and children (now adults) at his funeral.

His clinical and research interests were wide-ranging and included: diabetic pregnancy; hypoglycaemia in the neonate; feeding the newborn—he developed one of the first breast milk banks in the country; hyaline membrane disease; infection, including cross infection between babies; the use of corticosteroids to prevent respiratory distress syndrome; and transport of the sick pre-term baby.

Harold understood how important it was to share the knowledge and expertise of the unit and to engage and enthuse the next generation of neonatal intensive care specialists—both nurses and doctors. He was an exceptional mentor and committed teacher.

He retained an international perspective, visiting and advising neonatal units in many countries, and encouraging colleagues to visit and learn from the medical and nursing expertise at King's College Hospital. He went on to develop strong working and teaching links with some of these units, particularly in Lebanon and Greece. With Greece this turned into a 15 year love affair with the country, its people, and history.

Having worked and grown up in a system of apartheid in Namibia—which was then a protectorate of South Africa—and with his own understanding of the effects of anti-Semitism, he had a tremendous passion for the abolition of oppression, a commitment to equality, and a determination to help those in need. When working in Namibia, Harold's great humanity and his ability to feel his way into the mindsets of others helped to defuse many crises caused by the deep racial tensions that existed at that time, and by the depredations of the apartheid regime, which meant that resources were scarce.

His Namibian and Jewish roots created the backdrop for lifelong interests in African and Jewish culture and history. He had a wide range of interests including art and music—appreciating a huge range from traditional African music, jazz, classical, and kletzma. He had also developed a medical approach to horticulture with a greenhouse drip system and post-holiday ward rounds, nurturing exotic seeds from the arid and beautiful landscape of Namibia.

Harold had a great love for his family, friends, and colleagues, but would treat all he met with warmth, respect, and interest. A colleague wrote after his death, "We first met you as a teacher and later you became an invaluable friend, but mainly you were the person who reminded us that we were not alone."

He will be missed greatly by his wife, Sheila; his four children; 10 grandchildren; and family and friends from around the world. [**Mandy Gamsu and the Gamsu family, with contributions from colleagues**

]

This article

- **Full text**
- **Respond to this article**

Services

BMJ 2004;329:1347 (4 December), doi:10.1136/bmj.329.7478.1347-a

Obituary

Harold Gamsu

A pioneer in the development of neonatal intensive care

During the 30 years that Harold Gamsu spent as professor of neonatology at King's College Hospital, London, the hospital's neonatal unit became a nationally recognised centre of excellence. Harold also established a need for regional neonatal services and was instrumental in developing centres of excellence outside London.

He was a founding member and the first chairman of the South East Thames Regional Perinatal Monitoring Group, which guided developments in services and sought to achieve consensus for major projects, such as the introduction of the first computer system for neonatal and maternal care.

Harold also drove forward and chaired the South East Thames Confidential Review into Perinatal Deaths from 1987 to the advent of the national Confidential Enquiry into Stillbirths and Deaths in Infancy in 1992. He was instrumental in securing a regional study into the causes, management, and outcome of low birth-weight babies, which has accumulated many years of data, and he initiated a national survey on necrotising enterocolitis. He also developed one of the first breast milk banks in the country.

After qualifying he worked at the African State Hospital in Windhoek, Namibia. He began his training in paediatrics at Sheffield Children's Hospital and then moved to Ohio, United States, to work at the Cleveland Metropolitan General Hospital. He returned to Namibia before taking up posts at King's College Hospital, London.

He leaves a wife, Sheila; four children; and 10 grandchildren.

Harold Gamsu, professor of neonatology King's College Hospital, London, 1965-93 (b Windhoek, Namibia, 1931; q Witwatersrand, South Africa, 1954; FRCP Ed, FRCP), died on 31 August 2004 from complications following abdominal surgery.

[Mandy Gamsu]

Longer versions of these obituaries are available on bmj.com

Wendy Kutner

To: Dr Dino A. Giussani
Subject: RE:

Dear Dr Giussani
THank you for your e-mail. We are pleased that you are able to attend and have added your name to the list of participants.
We look forward to seeing you at the meeting.
With best wishes
Daphne Christie

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
The Wellcome Trust Centre
for the History of Medicine at UCL
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24 Eversholt Street
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Tel: 020 7679 8106
Fax: 020 7679 8193
w.kutner@ucl.ac.uk
www.ucl.ac.uk/histmed

-----Original Message-----
From: Dr Dino A. Giussani [mailto:dag26@cam.ac.uk]
Sent: 17 May 2004 15:22
To: w.kutner
Subject:

Dear Mrs Wendy Kutner,

Could you please book me a place at the Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth Witness Seminar to be held on Tuesday 15 June 2004. I would be delighted to attend and I thank the organisers for the invitation.

With best wishes,

Dino Giussani

Dr Dino A. Giussani, M.A., Ph.D
University Lecturer
Fellow of The Lister Institute for Preventive Medicine
Director of Studies in Medicine, Tutor and Fellow of Gonville & Caius College

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16 June 2004

Dear Dr Giussani

The Wellcome Trust History of Twentieth Century Medicine Group Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with pretern birth

May I say on behalf of The History of Twentieth Century Medicine Group and the co-organiser, how grateful we are to you for your contributions to yesterday's meeting? It really was a splendid occasion, and we hope that you enjoyed it as much as those of us who were observers.

As mentioned in previous correspondence and at the meeting, the taped proceedings of the meeting will now be sent for transcription, and we hope to have a draft manuscript to send you in about six months time for your comments. Ultimately we intend to publish an edited version of the proceedings, and you will be sent a copyright assignment form and final proof before publication.

Yours sincerely

Daphne Christie

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

The Wellcome Trust Centre for the History of Medicine at University College London is funded by the Wellcome Trust, which is a registered charity, no. 210183. Histmed logo images courtesy *Wellcome Library*, London.

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Dr Daphne Christie
The Wellcome Trust
24, Eversholt Street
London NW1 1AD

20 January 2005

Dear Dr Christie,

Please find enclosed the amended document and the signed copyright forms. I have also enclosed a published paper, in which Figure 1 shows how antenatal glucocorticoid therapy, in doses and dose intervals relevant to human clinical practice, can also have maturational effects on basal and stimulated cardiovascular function in the fetus. Finally, a short biographical sketch appears below.

With best wishes,

Dino A. Giussani

Biosketch

Dino A. Giussani was born in 1967. He obtained a PhD in Fetal Medicine at UCL and has worked at the University of Chile and Cornell University during Post-Doctoral Fellowships. He was appointed to a University Lectureship at the University of Cambridge in 1993. In 2001, he also became a Fellow of The Lister Institute for Preventive Medicine. Currently, he is a Reader in Developmental Cardiovascular Physiology & Medicine at the University of Cambridge and Director for Studies in Pre-Clinical Medicine at Gonville & Caius College, of the same institution.

corrected 1/6/05

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****

1. NAME Dr Dino Giussani

2. ADDRESS
   Department of Physiology,
   University of Cambridge, Downing Street
   CAMBRIDGE CB2 3EG

3. WITNESS SEMINAR: Prenatal Corticosteroids for Reducing Morbidity and Mortality
   15 June 2004

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GIUSSANI

PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY

The transcript of a Witness Seminar held by the Wellcome Trust Centre for the History of Medicine at UCL, London, on 15 June 2004

EDITED BY D A CHRISTIE AND E M TANSEY

Corrected 1/6/05.

Participants

Dr Mary Ellen (Mel) Avery
Sir Christopher Booth
Dr Peter Brocklehurst
Sir Iain Chalmers
Professor Patricia Crowley
Professor John Gabbay
Professor Harold Gamsu*
Dr Gino Giussani
Mrs Gill Gyte
Dr Stephen Hanney
Professor Jane Harding
Dr John Hayward
Dr Edmund Hey (Chair)
Dr Ian Jones
Professor Richard Lilford
Professor Miranda Mugford
Mrs Brenda Mullinger
Professor Ann Oakley
Dr Sam Richmond
Dr Roger Verrier Jones
Professor Dafydd Walters
Mr John Williams

DINO GIUSSANI

*Died 2004

the issues about clinicians using multiple courses of steroids, that their threshold for starting antenatal steroids is lower because if they are wrong, and the woman doesn't deliver soon, they can always give a second course. If you restrict people to giving a single course of steroids they may delay starting until there are stronger evidence, if you like, of impending preterm birth. So the groups of women selected into these trials is interestingly quite different I think in the current steroid group than the single steroid group, and that will make the interpretation of the results interesting.

Lilford: I was looking at the debate of my 14-year-old daughter about whether history is just an interesting thing to read, or whether it helps us to design our own futures, and listening to Jane speak makes me think that there really are occasions when history really does have a lesson for the future. Listening to you speak about finding these records was very interesting, but people were amazed in this room that you really could find those source materials after 30 years, and that you could find the trial documents and so on. When Harold moves the documents in his office, goodness knows where they might go. So the lesson that we might want to learn from this is the importance of some sort of systematic paid for archive for trial information and I don't know if you might want to comment. I know that the ESRC on their precious data sources do archive them and build into the grant the cost of so doing and the more I listen the more I think this might be something we ought to try to take forward as a matter of some urgency.

Chalmers: Very briefly. The MRC has got a working paper under the chairmanship of Peter Dukes that is in fact creating circumstances, group pilots, through which it would be possible for anyone receiving an MRC grant to archive their data. So at least biomedicine is catching up with the social scientists.

Dr ~~Gino~~ Giussani: I wanted to draw together some many comments, in particular one made by Iain Chalmers as to how do we translate evidence that we find in animal studies to the human situation. We haven't talked about many of the more subtle effects of antenatal glucocorticoid therapy that may prove detrimental in the long term to the adult. In the animal, there is overwhelming evidence now, accumulating evidence, that antenatal steroid therapy in doses, ~~in~~ and ~~those~~ dose intervals, used in human clinical practice today, have detrimental effects on the development of the adrenal gland. For example, fetuses that have been treated by steroids have an overreactive adrenal function, which may lead to long-term consequences ~~in the~~ in adult life. We have not talked about ~~other~~ maturational effects on other systems, such as the cardiovascular system. We know that glucocorticoids in fetal life increase blood pressure in a sustained manner, at a time that mechanisms that are ~~controlling~~ going to control the blood pressure ~~are being laid down~~ of the individual are being programmed in adult life, ~~to control blood pressure for long life~~, such as baroreceptors. We have evidence that antenatal glucocorticoid therapy reset the arterial baroreceptors to run or to maintain blood pressure at a greater level. And of course we don't know whether that would lead eventually

to detrimental effects. We all agree that glucocorticoids are life-savers, but we ~~cannot~~ have to begin to think as to whether some of these more fine-tuned side-effects may ~~be~~ become detrimental in later life. And I was just wondering whether we are going to get to talk about that later on, as to perhaps think of ~~fine-tuning~~ refining some of the dosing ~~of the~~ regimens of glucocorticoid therapy today, in an effort to maintain the beneficial effects, but to "weed out" the unwanted, adverse side-effects.

Harding: If I can make a very brief comment about that? This is another example of a new question for which the old data already had the answers. The blood pressure of the six-year-old children was recorded, but never analysed and published, and it will be published very shortly in Paediatrics, because we found the archives in the roof of the hospital, dragged them down, and said would you mind if we analysed these and published them? There is no difference in blood pressure at six years or, incidentally, at 30 years, but I think the issue for this conference again is one of new questions to which old data actually has the answer.

Dr John Hayward: I just wonder whether it's an opportunity if we are looking at getting research into practice, which is one of the future topics after we have had our tea break, just to hold in our mind some of the questions that have been raised. Interestingly, when I, and other people in this room, who knew me 40 years ago, one person talked as a medical student, another I applied as a job and didn't get, something went wrong, my fellow applicant got the job that he hadn't applied for, and I got the job that he applied for. It was bizarre. It's

nice to see Sir Christopher Booth here, who I never did work for eventually. Interestingly, I also worked with Cliff Robertson when he was a paediatrician at Hillingdon Hospital and was having difficulty in getting a job. The thing that strikes me is one of these interesting things as I have hovered in my own career as that of a GP, then getting interested in systematic reviews, training in public health, and coming back to public health, rather a weird career, dotting a lot of the lines, the same issues keep cropping up. There's always a concern: have we looked at the subjects right? What will the long-term detrimental effects be? Everybody's actually influenced by some horror that they have come across. And that's perhaps not so much the case for steroids, but it's certainly true if you look at the extent of the .....[?] breech presentation for example. My statement later will be about how we looked at getting research and practice and values to it. I think the danger is everybody worrying about some rare outcomes some 30 years hence as justification for sitting on your hands and not doing anything. The outcome of interest here was death, compared with survival, and I think that's the critical thing that's held in our minds and presumably there are children now, adults, who would not be here at all if their mothers hadn't consented to take part in the original trials and been fortunate enough to have the coin fall on their side and they actually got the intervention rather than the control, and I would have thought that those adults who are now alive would accept a certain amount of hypertension or some other problem as an alternative to not being here at all.

in 1965, then Senior Lecturer, Reader in Paediatrics and Director of the Neonatal Unit, 1979, and in 1994 Professor of Neonatology, later Emeritus. He established the London Perinatal Group in the 1970s, later known as the Thames Regional Perinatal Group.

Dr Dino Giussani

Mrs Gill Gyte

Dr Stephen Hanney

Professor Jane Harding

Dr John Hayward

Dr Edmund Hey

FRCP (b. 1934) trained as a respiratory physiologist in Oxford and worked for the MRC with Kenneth Cross, Geoffrey Dawes and Elsie Widdowson for some years before moving to Newcastle to get a grounding in paediatrics in 1968. He returned briefly to London in 1973 as a consultant to set up a respiratory intensive care service at Great Ormond Street Hospital, London, but returned to Newcastle in 1977 when the town's first neonatologist, Dr Gerald Neligan, died of leukaemia. Epidemiology and the conduct of controlled clinical trials have been his main research interests in recent years.

Professor Ross Howie

Dr Ian Jones

Professor Richard Lilford

Professor Sir Graham (Mont) Liggins

Professor Miranda Mugford

Mrs Brenda Mullinger

Professor Ann Oakley

Dr Sam Richmond

Dr Roger Verrier Jones

Professor Dafydd Walters

Mr John Williams

Giussani

see pages 57-68
Biographical note: 114 / Changes made ✓

PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY IN PRETERM BIRTH

The transcript of a Witness Seminar held by the Wellcome Trust Centre for the History of Medicine at UCL, London, on 15 June 2004

Edited by L A Reynolds and E M Tansey

11.8.05

-3 10.3.05; -4 7.07.05; -5 28.7.05;-6 4.8.05 (2nd); printed: 5 August 2005

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Corrected 21/9/05 ✓
Spare pages Removed 21/9/05
7/9/05
Rec'd back 9/9/05 ✓
Please return by 7 Sept 05

Prenatal Corticosteroids for Reducing Morbidity and Mortality In Preterm Birth

Participants

Dr Mary Ellen (Mel) Avery
Sir Christopher Booth
Dr Peter Brocklehurst
Sir Iain Chalmers
Dr Patricia Crowley
Professor John Gabbay
Professor Harold Gamsu†
Dr Dino Giussani
Mrs Gill Gyte
Dr Stephen Hanney
Professor Jane Harding
Dr John Hayward
Dr Edmund Hey (Chair)
Dr Ian Jones
Professor Richard Lilford
Professor Miranda Mugford
Mrs Brenda Mullinger
Professor Ann Oakley
Dr Sam Richmond
Dr Roger Verrier Jones
Professor Dafydd Walters
Mr John Williams

Among those attending the meeting:

Professor Richard Beard, Dr Sheila Duncan, Professor Abby Fowden, Dr Anita Magowska, Dr John Muir Gray, Professor Alison Macfarlane, Dr David Paintin, Professor Maureen Young

Apologies include:

Professor Sir Robert Boyd, Dr Clive Dash, Professor Geoffrey Chamberlain, Dr Pamela Davies, Professor Sir Liam Donaldson, Professor Peter Dunn, Dr Jonathan Grant, Professor Aidan Halligan, Professor Mark Hanson, Professor Ross Howie, Professor Frank Hytten, Professor Marc Keirse, Professor Sir Graham Liggins, Dr Jerold Lucey, Professor Sally MacIntyre, Dr Jonathan Mant, Professor Jim Neilson, Dr Cliff Roberton, Ms Barbara Stocking, Dr Peter Stutchfield, Dr Peter Williams, Professor Mark Walport, Professor Jonathan Wigglesworth

†Died 31 August 2004

Chalmers: The MRC has a working party under the chairmanship of Peter Dukes, which is creating circumstances through which it would be possible for anyone receiving an MRC grant to archive their data.[90] So biomedicine is catching up with the social scientists.

Dr Dino Giussani: I wanted to draw together some of ~~many~~ the comments, in particular one made by Iain Chalmers as to how do we translate evidence that we find in animal studies to the human situation. We haven't talked about many of the more subtle effects of antenatal glucocorticoid therapy that may prove detrimental in the long term to the adult. In the animal, there is overwhelming evidence now accumulated that antenatal steroid therapy, in [redacted] doses and dose intervals, used in human clinical practice today, have detrimental effects on the development of the adrenal gland. For example, fetuses that have been treated by steroids have an overreactive adrenal function, which may lead to ~~long-term~~ detrimental consequences in adult life. We have not talked about maturational effects on other systems, such as the cardiovascular system. We know that glucocorticoids in fetal life increase blood pressure in a sustained manner, at a time that mechanisms that are going to control the blood pressure of the individual in adult life are being programmed, such as ~~b~~the baroreceptors. We have evidence that antenatal glucocorticoid therapy reset the arterial baroreceptors to run or to maintain blood pressure at a greater level. And of course we don't know whether that would lead eventually to detrimental effects. We all agree that glucocorticoids are life-savers, but we have to begin to think as to whether some of these more ~~fine-tuned~~ subtle side-effects may become detrimental in later life.

I was also wondering whether we will talk later about refining some of the dosing ~~of the regiments~~ regimens of glucocorticoid therapy today, in an effort to

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the Joint Information Systems Committee (JISC) of the Higher Education Funding Councils and the University of Essex.

[90] Iain, any update on this?

22/9/05

maintain the beneficial effects, but to 'weed out' the unwanted, adverse side-effects.

Harding: If I can make a very brief comment about that? This is another example of a new question for which the old data already had the answers. The blood pressure of the six-year-old children was recorded, but never analysed and published, and it will be published very shortly in *Paediatrics.*[91] We found the archives in the roof of the hospital, dragged them down, and said, 'Would you mind if we analysed these and published them?' There is no difference in blood pressure at six years or, incidentally, at 30 years, but I think the issue for this conference again is one of new questions to which old data actually has the answer.

Dr John Hayward: I wonder whether this is an opportunity to look at getting research into practice, one of the future topics after the tea break, just to hold in our mind some of the questions that have been raised.

What strikes me is that during my own career as GP – becoming interested in systematic reviews, training in public health, and then returning to public health – the same issues keep cropping up. There is always a concern whether we have looked at the subjects correctly? What will the long-term detrimental effects be? Everybody is actually influenced by some horror that they have come across. That's perhaps not so much the case for steroids, but it's certainly true if you look at the external cephalic version (ECV) of breech presentation, for example. My statement later will be about how we looked at getting research evidence into practice. I think the danger is that everyone worries about some rare outcomes 30 years hence as justification for sitting on your hands and not doing anything. The outcome of interest here was death,

[91] Dalziel S R, Liang A, Parag V, Rodgers A, Harding J E. (2004) Blood pressure at six years of age after prenatal exposure to betamethasone: follow-up results of a randomized, controlled trial. *Pediatrics* 114: e(lectronic)373–7.

Sir Iain Chalmers

FRCPE FFPH FMedSci (b. 1943) has been Editor of the award-winning James Lind Library since 2003. He was Director of the UK Cochrane Centre in Oxford from 1992 to 2002 and Director of the National Perinatal Epidemiology Unit, Oxford, from 1978 to 1992. See www.jameslindlibrary.org/ (visited 2 June 2005).

Professor Archie Cochrane

CBE MBE FRCP FFCM (1909–88), medical scientist and epidemiologist, whose first clinical trial was conducted as a prisoner of war in Salonika. Following the war he was appointed to the Medical Research Council's Pneumoconiosis Research Unit in 1948. In 1960 he was appointed David Davies Professor of Tuberculosis and Diseases of the Chest at the Welsh National School of Medicine, Cardiff, becoming Director of the Epidemiology Research Unit there in 1961 until his retirement in 1974. His papers are available for study at the Cochrane Archive, Llandough Hospital, Penarth, Cardiff. See Cochrane (1976); Cochrane [ALC] (1988). See also Ness *et al.* (2002).

Dr Patricia Crowley

FRCOG FRCPI (b 1951) has been a consultant Obstetrician Gynaecologist at the Coombe Women's Hospital, Dublin, and Senior Lecturer at the Department of Obstetrics and Gynaecology, Trinity College Dublin since 19xx.

Dr Clive Dash

FFPM (b. 1940) graduated from University of Birmingham and did post-graduate obstetrics with Professor Hugh McLaren in Birmingham, and has spent most of his professional life in clinical research within the pharmaceutical industry. He instigated and coordinated the UK trial of antenatal steroids in 1974 while working as a clinical research physician for Glaxo in the UK. He has been an independent consultant in healthcare and pharmaceutical medicine since xxxx, while continuing his clinical practice in thoracic medicine.

Professor Geoffrey Dawes

CBE FRCOG FRCP HonFACOG FRS (1918–96), qualified at Oxford in 1943, spent a year? at Harvard in 1946. He was Director of the Nuffield Institute for Medical Research, Oxford, from 1948 to 1985., as well as a Governor of Repton, 1959–88, and Vice President of the Royal Society, 1976–77. See Liggins G (1998). Geoffrey Sharman Dawes, *Biographical Memoirs of Fellows of the Royal Society* 44: 110–25.

Professor John Gabbay

FFPHM (b. 1949) qualified in medicine at Manchester in 1974. After working on the social origins of medical knowledge for seven years at the University of Cambridge, he trained in public health and carried out qualitative research on NHS management and clinical audit in the 1980s. From 1992 until his retirement in 2004 he was Professor of Public Health and Director of the Wessex Institute of Health Research and Developmentat the University of Southampton, which houses the National Coordinating Centre for Health Technology Assessment, of which

he was former director. His recent research has focused on the implementation of evidence in clinical practice.

Professor Harold Gamsu

FRCP FRCPCH (1931–2004) graduated in Johannesburg in 1954. His training in paediatrics commenced there, and continued at the University of Sheffield and xx in Cleveland, Ohio. He was appointed as Wates Fellow at King's College Hospital, London, in 1965, then Senior Lecturer, Reader in Paediatrics and Director of the Neonatal Unit, 1979, and in 1994 Professor of Neonatology until his retirement in xxxx, later Emeritus. He established the London Perinatal Group in the 1970s, later known as the Thames Regional Perinatal Group.

Dr Dino Giussani

PhD (b. 1967) received his PhD in Fetal Medicine at UCL and has conducted post-doctoral work at the University of Chile and Cornell University. He was appointed university lecturer at the University of Cambridge in 1993; has been Fellow of the Lister Institute for Preventive Medicine there, since 2001 and a Reader in Developmental Cardiovascular Physiology and Medicine since ~~1998~~ 2004 and Director for Studies in Pre-clinical Medicine at Gonville and Caius College, Cambridge, since ~~200x~~ 2000.

Mrs Gill Gyte

MPhil (b. 1948) has been an antenatal teacher with the National Childbirth Trust (NCT) since 1985. She was a volunteer worker on the NCT Research and Information Group from 1990 to 1997 and has been the Consumer Panel Coordinator for the Cochrane Pregnancy and Childbirth Group since 1997.

Dr Stephen Hanney

PhD (b. 1951), trained as a political scientist, has specialized in examining evaluation and policy making in higher education and research. Since 1993 he has worked with [Professor] Martin Buxton at the Health Economics Research Group, Brunel University, London, developing and applying techniques of assessing payback or benefit from health research.

Professor Jane Harding

ONZM DPhil FRACP FRSNZ (b. 1955) obtained her medical degree at the University of Auckland in 1978 and completed a DPhil in fetal physiology at the University of Oxford in 1982. After specialist paediatric training in New Zealand and a postdoctoral fellowship at the University of California at San Francisco, she joined the faculty of xx at the University of Auckland in 1989 and was appointed Professor of Neonatology in 1997. She works as a specialist neonatologist at National Women's Hospital. She also heads the fetal physiology laboratory and is Deputy Director of the Liggins Institute at the University of Auckland.

Dr John Hayward

FFPH(b. 1946) was in general practice for 16 years before re-training in public health. From 1994/6 he led the Effective Care Project in maternity services for the Camden and Islington Health Authority.

Dr Jonathan Grant
Research Leader and Associate Programme Director
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19th March 2004

Dear Dr Grant

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004
2.00 pm – 6.00 pm

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is organising a Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15th June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1 2BE. Dr Edmund Hey has kindly agreed to chair the meeting and Sir Iain Chalmers is assisting us in the organisation.

Sir Iain Chalmers has recommended that we invite you to this meeting and we would be delighted to have you join us.

These seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history. I enclose a copy of the introduction to the first volume of our published transcripts, which will tell you a little more about these seminars, and a flyer of our recent publications to illustrate the range of topics we cover.

Continued/... Page 2

We are in the process of inviting senior scientists, clinicians, and representatives from relevant organisations to attend the meeting and hope to promote a lively discussion.

We will be providing further details in due course and would particularly appreciate, at this stage, suggestions of possible participants.

I look forward to hearing from you and do hope you will be able to accept this invitation.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

Wendy Kutner

To: jgrant@rand.org
Cc: Daphne Christie; Chalmers, Sir Iain
Subject: Witness Seminar: 15 June 2004 - Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth


CORTIgrantinvlt.doc


DRAFTcorticoFLYER190404.doc


WHATIS--april2004revdc.DOC

Dear Dr Grant, I attach an invitation to the above meeting and have left a voice message on your mobile alerting you to the fact that I am sending you this e-mail. We do hope you will be able to attend.
Yours sincerely, Wendy Kutner

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
The Wellcome Trust Centre
for the History of Medicine at UCL
Euston House
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21 April 2004

Dear Dr Grant

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 30th March 2004 2.00 pm – 6pm

We wrote to you on 19th March, inviting you to attend the above meeting. As we have not had a reply, but have been experiencing difficulties with our post, our original letter, or your reply, may therefore have gone astray. We enclose a copy of that letter and look forward to hearing from you.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

The Wellcome Trust Centre for the History of Medicine at University College London is funded by the Wellcome Trust, which is a registered charity, no. 210183. Histmed logo images courtesy *Wellcome Library*, London.

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Dr Jonathan Grant
Research Leader and Associate Programme Director
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27 April 2004

Dear Dr Grant

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004 2.00 pm – 6pm

We wrote to you on 21st April, enclosing our original invitation letter to the above meeting, but the date of the meeting on the reminder letter was incorrect. Please note that the date of the meeting is Tuesday 15th June 2004.

Yours sincerely

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey

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Wendy Kutner

To: Iain Chalmers
Cc: Daphne
Subject: RE: Witness Seminar: 15th June 2004 - Prenatal corticosteroids

Dr Jonathan Grant has just telephoned to say that he is unable to attend as he has a Board meeting in Amsterdam at the same time. Wendy

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
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-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 29 April 2004 14:44
To: 'w.kutner@ucl.ac.uk'
Cc: Daphne; Edmund Hey
Subject: RE: Witness Seminar: 15th June 2004 - Prenatal corticosteroids

Dear Wendy

Here are contact details for the three people who may not have received your initial invitation.

Best wishes, Iain

Dr Nicholas Hicks
Director of Public Health
Milton Keynes, Primary Care Trust
Hospital Campus, Standing Way
Eaglestone
Milton Keynes
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nicholas.hicks@mkpct.nhs.uk
sue.gardiner@mkpct.nhs.uk

Dr John Hayward
Director of Public Health
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Directorate of Public Health
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Dr Alison Hill
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Fax. 226959
alison.hill@phru.nhs.uk

-----Original Message-----
From: Wendy Kutner [mailto:w.kutner@ucl.ac.uk]
Sent: 27 April 2004 13:01
To: Edmund Hey; Chalmers, Sir Iain
Cc: Daphne
Subject: Witness Seminar: 15th June 2004 - Prenatal corticosteroids

Dear Sir Iain and Dr Hey, Further to my e-mail and attached list which I sent you both this morning, I attach another list which I have updated to include those attending and apologies, which you requested. Please note that Mrs Brenda Mullinger, a suggestion by Professor Gamsu, was not on the previous list I sent you. I hope to send flyers later today or tomorrow.
Wendy

Mrs Wendy Kutner
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25 March 2004

Dear Dr Gray

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004
2.00 pm – 6.00 pm

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is organising a Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15th June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1 2BE. Dr Edmund Hey has kindly agreed to chair the meeting and Sir Iain Chalmers is assisting us in the organisation.

Sir Iain Chalmers has recommended that we invite you to this meeting and we would be delighted to have you join us.

These seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history. I enclose a copy of the introduction to the first volume of our published transcripts, which will tell you a little more about these seminars, and a flyer of our recent publications to illustrate the range of topics we cover.

Continued/... Page 2

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We will be providing further details in due course and would particularly appreciate, at this stage, suggestions of possible participants.

I look forward to hearing from you and do hope you will be able to accept this invitation.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

rec 20/4/04 acc 21/4/04

INSTITUTE OF HEALTH SCIENCES

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University of Oxford
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31 March 2004

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey
The Wellcome Trust Centre for the History of Medicine
University College London
24 Eversholt Street
London NW1 1AD

Dear Dr Christie,

The Wellcome Trust's History of Twentieth Century Medicine Group Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth. 15 June 2004

Thank you very much for inviting me to participate in this meeting. I am pleased to accept and look forward to the event.

Yours sincerely,

J A Muir Gray, CBE, DSc, MD, FRCP, FRCPSGlas, FCILIP

The Wellcome Trust Centre for the History of Medicine at University College London

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26 April 2004

Dear Dr Muir Gray

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004, 2pm–6pm

We are delighted that you are able to attend the above meeting and are happy to tell you that plans are proceeding well. A copy of our publicity material is enclosed and I will be sending you a draft programme in due course. A full attendance list will be available at the meeting.

We will be asking some participants to "start the ball rolling" by saying a few words on specific subjects, as we like to prime a few people to lead off the discussions, although there will be ample opportunity to contribute throughout the meeting. We do not show slides or overheads at the meetings, as we wish to encourage informal interchange and conversation. If however, you would like any material to be available to the audience, we could photocopy a diagram or article for you, and leave a copy on every chair.

Please do not hesitate to contact either myself or Mrs Wendy Kutner 020 7679 8106 if you have any queries prior to the meeting.

We very much look forward to seeing you at the meeting.

Yours sincerely

pp **Dr Daphne Christie**
Senior Research Assistant to Dr Tilli Tansey

enc.

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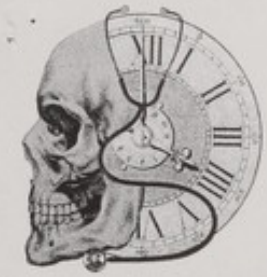

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25 March 2004

Dear Dr Gray

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004
2.00 pm – 6.00 pm

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Sir Iain Chalmers has recommended that we invite you to this meeting and we would be delighted to have you join us.

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Continued/... Page 2

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Yours sincerely

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Senior Research Assistant to Dr Tilli Tansey

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21 April 2004

Dear Dr Gray

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 30th March 2004 2.00 pm – 6pm

We wrote to you on 28th March, inviting you to attend the above meeting. As we have not had a reply, but have been experiencing difficulties with our post, our original letter, or your reply, may therefore have gone astray. We enclose a copy of that letter and look forward to hearing from you.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

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27 April 2004

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Tuesday 15th June 2004 2.00 pm – 6pm

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Yours sincerely

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey

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29 April 2004

Dr Gray

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004
2.00 pm – 6.00 pm

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is organising a Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15th June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1. Dr Edmund Hey has kindly agreed to chair the meeting and Sir Iain Chalmers is assisting us in the organisation.

Sir Iain Chalmers has recommended that we invite you to this meeting and we would be delighted to have you join us.

These seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history. I enclose a copy of the introduction to the first volume of our published transcripts, which will tell you a little more about these seminars, and a flyer of our recent publications to illustrate the range of topics we cover.

Continued/... Page 2

The Wellcome Trust Centre for the History of Medicine at University College London is funded by the Wellcome Trust, which is a registered charity, no. 210183. Histmed logo images courtesy *Wellcome Library*, London.

We are in the process of inviting senior scientists, clinicians, and representatives from relevant organisations to attend the meeting and hope to promote a lively discussion. We will be providing further details in due course and would particularly appreciate, at this stage, suggestions of possible participants.

I look forward to hearing from you and do hope you will be able to accept this invitation.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

Wendy Kutner

To: s.gray@doh.gov.uk × mail returned
Cc: Daphne; Chalmers, Sir Iain
Subject: Witness Seminar: 15 June 2004 - Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth

WHATIS--april2004revdc.DOC CORTICOSelinaGrayinvltr.doc DRAFTcorticoFLYER190404.doc

Dear Dr Gray

Please find attached an invitation to the above meeting, which we hope you will be able to attend. A hard copy of this invitation will be sent to you in the post today. A previous invitation was sent on 25th March to the wrong address. Yours sincerely,
Wendy Kutner

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
The Wellcome Trust Centre
for the History of Medicine at UCL
Euston House
24 Eversholt Street
LONDON NW1 1AD

Tel: 020 7679 8106
Fax: 020 7679 8193
w.kutner@ucl.ac.uk
www.ucl.ac.uk/histmed

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 13 May 2004 12:45
To: Gray, Selena
Cc: Wendy
Subject: RE: Witness seminar on 15th June

Dear Dr Gray
We are sorry that you are unable to attend. We will keep you informed of the subsequent publication.
Yours sincerely
Daphne Christie

-----Original Message-----
From: Gray, Selena [mailto:Selena.Gray@uwe.ac.uk]
Sent: 13 May 2004 12:30
To: d.christie@ucl.ac.uk
Subject: Witness seminar on 15th June

Dear Dr Christie
Thank you for the kind invitation to the Witness Seminar on the 15th June. I would very much to have attended what sounds to be a very interesting event, but unfortunately I already have 3 other committments that day. Please convey my apologies to Iain Chalmers, and I hope the day goes well,
yours sincerely
Selena Gray

Dr Selena F Gray
Reader in Public Health & Director of the Centre for Research in Applied Health and Social Care
Email: Selena.Gray@uwe.ac.uk
Please note new telephone no: 0117 32 88849

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Faculty of Health and Social Care
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Telephone 0117 32 88849
email selena.gray@uwe.ac.uk

Mrs Gill Gyte
~~James Lind Library~~
The James Lind Initiative
~~Summertown Pavilion~~
~~Middle Way~~
~~OXFORD OX2 7LG~~

Dr Daphne Christie
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www.ucl.ac.uk/histmed
Tel: +44 (0) 20 7679 8125
Fax: +44 (0) 20 7679 8193

19th March 2004

Dear Mrs Gyte

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004
2.00 pm – 6.00 pm

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is organising a Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15th June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1 2BE. Dr Edmund Hey has kindly agreed to chair the meeting and Sir Iain Chalmers is assisting us in the organisation.

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Continued/... Page 2

We are in the process of inviting senior scientists, clinicians, and representatives from relevant organisations to attend the meeting and hope to promote a lively discussion.

We will be providing further details in due course and would particularly appreciate, at this stage, suggestions of possible participants.

I look forward to hearing from you and do hope you will be able to accept this invitation.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 01 April 2004 12:15
To: Gill Gyte
Cc: Wendy
Subject: RE: Wellcome Trust meeting on 15 June

Dear Gill
We are delighted that you are able to attend the Witness Seminar in June and will be sending further details in due course.
We look forward to receiving your suggestions of people.
With best wishes
Daphne Christie

-----Original Message-----
From: Gill Gyte [mailto:ggyte@cochrane.co.uk]
Sent: 01 April 2004 12:09
To: d.Christie@ucl.ac.uk
Subject: Wellcome Trust meeting on 15 June

Dear Daphne

Thank you for your letter of 19 March, which I only received at the beginning of the week. I am sorry for the delay in replying but I have been away.

I would very much like to attend the 'Witness seminar on Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15 June. It looks a very interesting way of gathering information and this has been an important topic for women and their families.

I have a couple of people whom you might like to invite too, I will get their contact details and get back to you.

best wishes
Gill

Gill Gyte
Consumer Panel Co-ordinator Cochrane Pregnancy and Childbirth Group
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England, UK
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UCL

Mrs Gill Gyte
Consumer Panel Co-ordinator Cochrane Pregnancy & Childbirth Group
'Oldfield'
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Dr Daphne Christie
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26 April 2004

Dear Mrs Gyte

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth
Tuesday 15th June 2004, 2pm–6pm

We are delighted that you are able to attend the above meeting and are happy to tell you that plans are proceeding well. A copy of our publicity material is enclosed and I will be sending you a draft programme in due course. A full attendance list will be available at the meeting.

We will be asking some participants to "start the ball rolling" by saying a few words on specific subjects, as we like to prime a few people to lead off the discussions, although there will be ample opportunity to contribute throughout the meeting. We do not show slides or overheads at the meetings, as we wish to encourage informal interchange and conversation. If however, you would like any material to be available to the audience, we could photocopy a diagram or article for you, and leave a copy on every chair.

Please do not hesitate to contact either myself or Mrs Wendy Kutner 020 7679 8106 if you have any queries prior to the meeting.

We very much look forward to seeing you at the meeting.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

enc.

The Wellcome Trust Centre for the History of Medicine at University College London is funded by the Wellcome Trust, which is a registered charity, no. 210183. Histmed logo images courtesy *Wellcome Library*, London.

The Wellcome Trust Centre for the History of Medicine at University College London

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16 June 2004

Dear Mrs Gyte

The Wellcome Trust History of Twentieth Century Medicine Group Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with pretern birth

May I say on behalf of The History of Twentieth Century Medicine Group and the co-organiser, how grateful we are to you for your contributions to yesterday's meeting? It really was a splendid occasion, and we hope that you enjoyed it as much as those of us who were observers.

As mentioned in previous correspondence and at the meeting, the taped proceedings of the meeting will now be sent for transcription, and we hope to have a draft manuscript to send you in about six months time for your comments. Ultimately we intend to publish an edited version of the proceedings, and you will be sent a copyright assignment form and final proof before publication.

Yours sincerely

Daphne Christie

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

The Wellcome Trust Centre for the History of Medicine at University College London is funded by the Wellcome Trust, which is a registered charity, no. 210183. Histmed logo images courtesy *Wellcome Library*, London.

THE WELLCOME TRUST

WITNESS SEMINARS

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****

1. NAME **Mrs Gill Gyte**

2. ADDRESS

Cochrane Pregnancy & Childbirth Group
'Oldfield'
159 Hardhorn Rd
Poulton-Le-Fylde
Lancashire FY6 8ES

3. WITNESS SEMINAR: **Prenatal Corticosteroids for Reducing Morbidity and Mortality**
15 June 2004

4. ASSIGNMENT

I confirm that I am the author and legal owner of my contribution to the proceedings of the Witness Seminar and of any comments I may have made on any draft transcript ("my Contribution"), and I assign to the Trustee of the Wellcome Trust ("the Trust") the copyright in my Contribution.

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7. USE OF MY CONTRIBUTION

I reserve the right to make use of my Contribution, having first obtained the permission of the Trust for me to do so (such permission not to be unreasonably withheld) and I confirm that in any such use I will acknowledge the Trust.

Signed Gill Gyte Date 24/1/05

Corrections are on pages

49
50
51
95

I am so very sorry this has taken me so long. So many other things to just mum.

best wishes

Gill

Gill Gyte
Oldfield
159 Hardhorn Road
Poulton Le Fylde
LANCASHIRE
FY6 8ES

Corrected 10/6/05

Mrs Gill Gyte BSc, MPhil (b 1948) has been an antenatal teacher with the National Childbirth Trust (NCT) since 1985, and still leads antenatal classes now. She was a volunteer worker on the NCT Research and Information Group from 1990 to 1997. Since 1997, she has been the Consumer Panel Co-ordinator for the Cochrane Pregnancy and Childbirth Group.

PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY

The transcript of a Witness Seminar held by the Wellcome Trust Centre for the History of Medicine at UCL, London, on 15 June 2004

EDITED BY D A CHRISTIE AND E M TANSEY

Participants

Dr Mary Ellen (Mel) Avery
Sir Christopher Booth
Dr Peter Brocklehurst
Sir Iain Chalmers
Professor Patricia Crowley
Professor John Gabbay
Professor Harold Gamsu*
Dr Gino Giussani
Mrs Gill Gyte
Dr Stephen Hanney
Professor Jane Harding
Dr John Hayward
Dr Edmund Hey (Chair)
Dr Ian Jones
Professor Richard Lilford
Professor Miranda Mugford
Mrs Brenda Mullinger
Professor Ann Oakley
Dr Sam Richmond
Dr Roger Verrier Jones
Professor Dafydd Walters
Mr John Williams

*Died 2004

Chalmers: I just wanted to comment on some themes which have come up about extrapolation from data in animals and if you like physiological data, or physiopathological data in humans and observational data in humans. I think one of the most remarkable things about Auckland was that Mont and Ross went directly from hypotheses they had tested in animals to see whether they were relevant to women. One of the things that gets me really annoyed is people working with animals who generate hypotheses whether it's about brain damage in the long time or some other sorts of things, but then do not exercise the self-discipline which Mont Liggins and Ross Howie did. I am going to give you one example that I came across in Oxford and it may be a little bit improper to speak ill of the dead, but I am going to tell you an anecdote about Geoffrey Dawes. Geoffrey Dawes was one of the hubs of perinatal physiological research in this country, and we often had arguments together along the lines that I have just been complaining about. I had the impression that he was very annoyed that he didn't make the discovery that Mont Liggins and Ross Howie made and I remember him in the 1990s, by which time I had moved to the Cochrane Centre, ringing me up in some glee, saying that he had discovered that steroids, this is an observational study, steroids had an apparent association with the pattern of fetal breathing movements, which he was very interested in. So I said to him, 'So what? You have now a mass of data from women and babies, if you have a hypothesis that's worth testing in terms of the relevance of your observations to human health, then test it, using the data, the mass of data that's now available from human experiments'. But there is this incredible lack of self-discipline where people who know how to design experiments in

animals actually don't know how to design them in human beings. They don't know how to design them or analyse them, as we have been hearing as a consequence of the dangers of sub-group analyses coming from someone faced with a statistically non-significant effect on death as it happened in the US collaborative trial. And it's just an example of very considerable scientific ill-discipline which Ross and Mont showed how well you could avoid. That's all.

Walters: Having done a lot of work in the lab and also done some clinical trials, I do lab work every time. It is very hard I think to do clinical trials because of the obstacles that are currently in our way, particularly in this country. I mean ethics committees, 60-page ethics forms, trying to get support from the institutions and even more European hurdles to get through even now, with having to record our clinical trials centrally. Also I think on a scientific basis, the variables in clinical trials are much more difficult to control than they are in the lab. So as a sort of humble physiologist trying to get into clinical work, give me the lab every time.

Avery: Just a note, Mark Liggins spent a sabbatical in Geoffrey Dawes lab and specifically told Dawes that he would not allow anyone to do any work, even discuss, surfactants for the whole time that Mark was there.

Hey: Well, that's straight from the horse's mouth.

Dr Avery: One petty observation, but I couldn't resist.

Hey: I will just interject that the Ross conference report that you mentioned in 1976, there are five papers from the USA saying that they tried to do a trial and it was too difficult. We moan now about trials being difficult. You go back, they have always been saying that they were difficult. I think they are more difficult, but it's always been so. Yet sometimes it goes very well.

Gyte: I am moving away ~~or~~ and back to a theme that was around before. As a consumer representative, I have always been very interested in the implementation of research findings, and my experience around this area came when I was a consumer representative on the ~~Oracle~~ ORACLE* trial, which was a trial looking at antibiotics in preterm labour. And in the development of the protocol, the researchers were wanting to do a second randomization of steroids within the main trial, and it was actually not our organization, the National Childbirth Trust (NCT), but another consumer organization, the Association for the Improvement in Maternity Services (AIMS), who very much put their foot down and said it was unethical to randomize women to steroids, and that actually all women should be given them within this multicentre trial and that second randomization was removed.

ORACLE - "A randomised multi-centred controlled trial of broad spectrum antibiotics for preterm labour or preterm prelabour rupture of membranes (pPROM)" Published - Lancet 2001 357

Hey: Just remind us of the date of the Oracle trial.

Gyte: I cannot quite remember. We are doing a seven-year follow up now, so it was 1995.

Hey: It was 1995, the results came out three years ago in the *Lancet*. The relevance is that one of the uncertainties that remains about steroid use is whether it is a wise thing to do for a mother's sake, when there is premature rupture of membranes, because you may, in doing something good for the baby, increase the risk of the mother developing a generalised septicaemia. So the people couldn't see that there was an unanswered question there presumably.

Effective Care in Pregnancy and Childbirth

Gyte: I went to ~~*Effective Campaigns in Childbirth*~~ and read Patricia's chapter to give an NCT perspective actually, and I remember thinking that there were some areas of uncertainty, but certainly that randomization was removed from the study.

Dr Peter Brocklehurst: I suppose I was just thinking about how we are now approaching antenatal steroids, how we have heard that it was very difficult to get antenatal steroids uptake, particularly in the

Effective Care in Pregnancy and Childbirth
1989. 50 Edit. Chalmers I, Enkin M + Keirse MJNC
Oxford University Press

UK, and then within a very short space of time, we were throwing it around like smarties, and I suppose what nobody has mentioned is that in order to get 90 per cent coverage of babies admitted to the neonatal unit, you have to give an awful lot of women antenatal steroids. I remember a lovely quote from ~~Jacque Alferich~~ (?) at Liverpool Women's Hospital. He said, 'If a woman under 34 weeks goes into Liverpool and burps, then she gets antenatal steroids'. They were giving so much of it, in order to get 95 per cent of babies admitted with steroids. And then the use of multiple courses of steroids, and now of course what's being considered more and more in the literature are the potential adverse effects, not just of multiple courses of steroids, but John Newnam's group which is coming up with evidence about the potential long-term hazardous effect of a single course of antenatal steroids on brain development. It's all very new stuff, but we may find ourselves going in a different direction to an extent. I think a lot of what is difficult about this issue, is that we are not very good at predicting preterm birth, and if we were better at predicting who was going to deliver preterm we would probably feel much more comfortable about using steroids in a much more targeted way. The concern is that currently probably at least 50 per cent of women who get antenatal steroids do not deliver preterm and therefore if there is long-term harm, it will be in those babies that will manifest it, and if we could target it better, we would probably all feel a bit more comfortable. So I just think we are beginning to go the other way, where people are actually being more cautious now with steroids than they were maybe even five years ago.

Zarko Alfirevic

Crowley: Could I remind you that in the Auckland trial a lot more babies died in the placebo group, and therefore the survivors of prematurity of that time should in fact be neurologically worse? That there should be a disadvantaged group on steroids, because a lot survived prematurity. So if you have those people at 30 years of age, and if there's no difference neurologically at age 30, then it's unlikely that they taking steroids single-dose was doing any harm.

Jane Harding: The number of comments I could make. I think you are quite right about the issue if you had to treat a lot of women. In fact if you look overall at the studies that we were able to put together in a systematic review, 40 per cent of women who were entered into the trial did not deliver after one week. So when you get into the issue of well how long did the effect last and what do you do with the women who've been treated and haven't delivered after a week, you have got a lot of women to consider.

To come back to the issue of ruptured membranes, and I think it is fair to say in the mid-1990s there was still confusion about the issue, but the solution was not to do a new trial. The solution was to go back to the old trials. There had been at that time over 4000 women randomized, and the data was present from the original trials, they had just never been analysed and in fact we in about 1994/5 and I cannot remember the exact date, but we had a debate around a clinical case at a clinical conference at my hospital, after which David Knight, who was the Director of the nursery at the time, said to me isn't that question answered. Surely the data must be there. Now just

indeed before surviving, and the anxiety that goes with that, those things haven't been made explicit and I suspect that if, we had hoped that there would be a woman here who had received corticosteroids, now I don't know what her history was at all, but I was certainly quite impressed by Barbara Stocking, who is now chief executive of OXFAM, saying that in her first pregnancy she delivered prematurely and her son went through a really rough time, she read Patricia's systematic review and in her second pregnancy she insisted that she should have steroids if she went into preterm labour again. She became a big advocate, and I have come across more than one mother, maybe Gill Gyte can enlighten us here, they have lobbied to have this, because they as parents actually think this is important, obviously because they are worried about their children, but so that they can perhaps have less to worry about themselves.

Gyte: I don't have any personal experience of antenatal classes, but I do not NTT does lobby very much to implement evidence, generally in terms to implement evidence-based care.

Oakley: This is slightly beside the point, or perhaps not, because I think this issue of the role of the users of health services and the extent to which they are demanding evidence is a very important one and it's something that we need to know more about. But of course one of the problems with that, or one of the issues in that area, is that first of all the product needs to be dissuaded from the belief that experts know what they are doing. I remember one of the early

projects that I worked on in 1974 involved an observational study of an antenatal clinic at a hospital in London which has of course got to be nameless, and I hung around this clinic for about a year observing what the doctors were doing, and I was absolutely astonished in my second week, I think there was a changeover the most junior doctors, and two of them came to me and they asked me what consultant X would recommend in a particular case, because they didn't know what they were supposed to be doing because they hadn't met their consultant yet. I didn't realize that the eight different consultants who ran this clinic all had different policies. I mean what I was doing was learning what those policies were, but then I was passing on this information to the junior members of their team, so that they could also practice non-evidence-based medicine. That was a long time ago, but I think it is still the case that many people believe that doctors and other experts know what they are doing. So another issue in all of this is about the epidemiological shift in people in general in society understanding that experts including those in other fields, and I spend a lot of my time at the moment with professors of education who don't believe in systematic reviews of the evidence. But it is about the role of the expert, and the relationship between research, evidence and the evidence and form of policy across a whole lot of different sectors.

Crowley: In 1985 as an obstetric senior registrar, I inherited a woman who was having an anti..... haemorrhage at 37 weeks as we thought, and we thought she was 37 weeks because the registrar who did her first antenatal visit had made a mistake about her dates. She was in fact 33 weeks and I delivered the baby in consultation with the

Lois Reynolds

From: Gill Gyte [ggyte@cochrane.co.uk]
Sent: 31 August 2005 15:34
To: l.reynolds@ucl.ac.uk
Subject: Witness Seminar: Prenatal Corticosteroids for Reducing Morbidity and Mortality in Preterm Birth, 15 June 2004

Dear Lois

Thank you for sending me the final proof of the above document. I have checked my parts are a are fine. I am not sure I can suggest any journals, sorry.

best wishes
Gill

Gill Gyte, National Childbirth Trust (NCT) Antenatal Teacher
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